ALBERT SZENT-GYÖRGYI MEDICAL UNIVERSITY

RENAMING CELEBRATION

10th—11th December
1987

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I. RENAMING CELEBRATION IN THE NATIONAL THEATRE OF SZEGED

10th December, 1987
11.00 a.m.

1.

PROFESSOR JÁNOS SZILÁRD

Opening speech

Honoured Guests!

On this remarkable day let me greet Károly Németh the President of the Presidium of the Hungarian People's Republic, the members of the Szent-Györgyi family here present, the representatives of the Diplomatic corps, the Ministry of Health and Cultural Affairs, the Hungarian Academy of Sciences, the representatives of the Communist Party, and state and social organizations of Szeged and Csongrád County. I also wish to welcome colleagues from Hungarian and foreign Universities, professors, honorary doctors, lecturers and students of our University.

Upon the request of the Council of the Szeged University of Medical Sciences, the Presidium of the Hungarian People's Republic has approved the renaming our University after Albert Szent-Györgyi who was the Head of the Department of Medical Chemistry between 1928 and 1945, as well as dean and rector of the University. I am convinced that any explanation is unnecessary why the Szeged University of Medical Sciences wishes to bear the name of Albert Szent-Györgyi. This decision, which was formulated even in Szent-Györgyi's lifetime, and cherished since then, was not prompted by actual interests but by firm and lasting principles and facts.

Scientific respect, the reputation of Albert Szent-Györgyi as well as his devotion to human mankind, progress and science and his sense of responsibility justify our wish. As John T. Edsall wrote in his obituary: "Albert Szent-Györgyi was a scientist and an incomparable humanitarian man". Szent-Györgyi himself wrote in his autobiography: "never has the World known an era more whirling than this, therefore, there has to come a paramount change in our ideas as well." "For me" he wrote "it is clear what this change is: It is a transition from a pre-scientific into a scientific era which is not only a fundamental change, but it has come unexpectedly without giving us time to adapt to it."

In his autobiography Szent-Györgyi wrote: "Is not science about living society? I believe it is. Science is first of all the society of people without any limitations in time or space. Science opens unlimited possibilities if we work together instead of pushing advantages at the expense of each other. Science has always helped in understading and dominating Nature. It will perhaps also help us to comprehend ourselves while a new way of human life is being created, the richness and beauty of which cannot be described even with the liveliest imagination."

The lifework and attitude of Albert Szent-Györgyi which have never seemed more up-to-date than nowadays, prompted us to decide to rename our University.

Opening of the Renaming Celebration in the National Theatre of Szeged — by Professor János Szilárd, Rector of the Medical University.

2.

KÁROLY NÉMETH

Presentation of the renaming document

Honoured University Council!
Ladies and Gentlemen!

I have the honour to greet all the Hungarian and foreign guests at this celebration. I wish to convey the best regards of our state and party leadership to the community of Szeged University of Medical Sciences.

I highly appreciate the kind invitation, and I am glad to have the opportunity to participate and contribute to this very important event in the life of the University. It is a great honour for me to have the pleasant duty of presenting the document entitling the University to use the name of Albert Szent-Györgyi — according to your wish.

The presidium of the Hungarian People's Republic readily supports this intention and believes that this renaming will also meet the concensus of the public. The name, the life work and the memory of Albert Szent-Györgyi are highly esteemed throughout Hungary. He remained loyal to his town and country declaring himself Hungarian, even when he lived and worked in the United States of America.

Efforts to serve mankind as well as affection towards his country were his main intentions. In his public and scientific activities alike he was always led by feelings of responsibility and humanity. I consider that this mentality is still worth following nowadays.

Honoured Guests!

It is now fifty years since Albert Szent-Györgyi received the Nobel prize. On the occasion of this remarkable Anniversary I present to you this document entitling the University to bear his name. I wish you to continue your work in his spirit, further enriching the results achieved so far and striving, at the same time, to benefit our people and country.

In this special hour I wish to greet all the staff and students of the University which bears here and now the name of Albert Szent-Györgyi. I wish you health, peaceful and constructive work.

Thank you for your attention.

Károly Németh, the President of the Presidium presents the renaming document to Professor János Szilárd, Rector

PROFESSOR BRUNÓ F. STRAUB

Remembering Albert Szent-Györgyi

Honoured Guests!

It is known that his years as professor in Szeged were the peak of Albert Szent-Györgyi's career and influence. An occasion like this — that is, when I have an opportunity to talk about my Master — is always a responsible and honorable duty.

This day, when Szeged University of Medical Sciences is being renamed Albert Szent-Györgyi University, not only has confirmed that he is one of the greatest sons of our country, but also that the University wishes to continue his work towards progress in science, congnition of truth, the training and education of the young, and cultural development in Hungary.

As a disciple and freshman I was lucky to work with him just at that period. Allow me to talk about my personal memories and how the University — first of all students — can and should follow his lead.

I was eighteen when Albert Szent-Györgyi asked me, a first year student, whether I felt like working at his Institute. During the years of training he checked my work personally, and in the next laboratory I could see myself how he worked with his co-worker dr. Ilona Banga. I am not going to talk about professional memories but about him as a human being.

The Professor talked to me as well as to other young research workers as if we had been his equals. And it was easy to get used to this and follow his example.

In the beginning of the 30's from a formal, hierarchic and authoritative atmosphere I entered a wonderful new world. Respect here was paid to one's work and human values and not to one's rank.

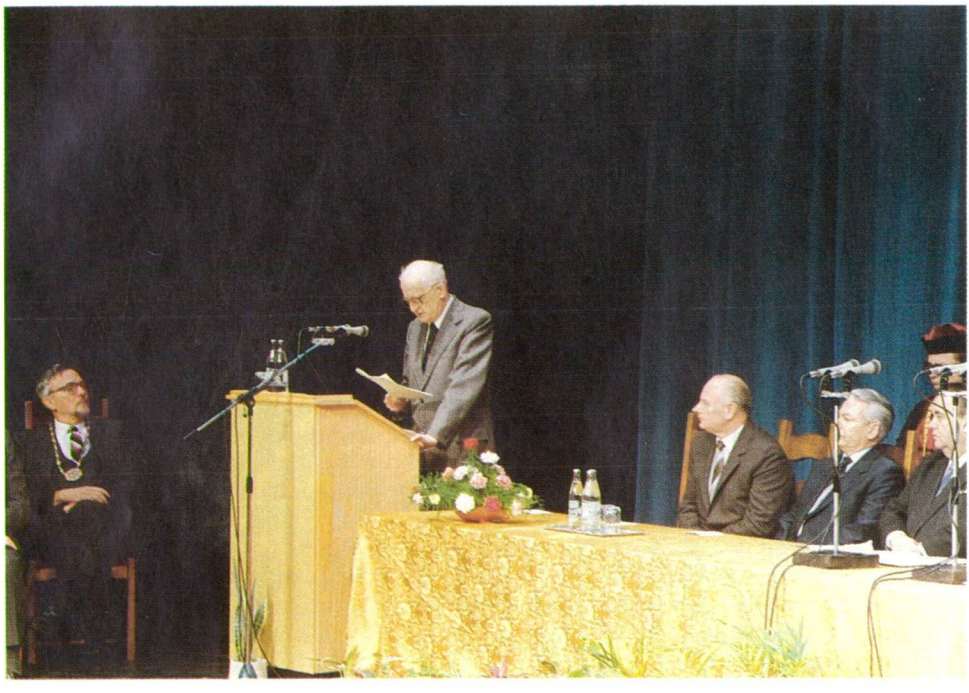
With the passing of years, we the younger generation started to contribute to the progress of research in the Department and two new elements could be observed. These were in contrast with those prevailing at other neighbouring Departments in Dom square. One of these elements was that whenever a new result was achieved Szent-Györgyi asked me to set it down in the form of a scientific paper. After long contemplation and "gnawing on the end of my pencil" I prepared the article and presented it to the professor. After a couple of days he gave the paper back in a form which was definitely more intelligible and logic than my original version. On the top of the paper my name appeared only, although the original idea and the final version of the manuscript came from the Master. One proof of Szent-Györgyi's greatness was that he never put his name on any paper the experimental results of which were not his own work. After four or five years, naturally I also learnt to come up with ideas and then put the results down comprehensibly. By then only minor amendments were necessary.

I feel it important to relate another of my memories. For Professor Szent-Györgyi the search after scientific truth, the recognition of hitherto unrevealed facts and relationships was a credo, the aim of his life. It happened many times that when he arrived in the laboratory in the morning he would immediately start to talk about his new ideas with whichever of his co-workers he happened to meet. He never expected them to respond merely with a remark on how interesting his idea was: rather he wanted to hear objections and arguments. He highly appreciated it if someone added new and constructive thoughts to his ideas. This kind of human contact, free of any kind of authoritativeness, was the most wonderful and in fact the most fruitful way of searching after scientific truth.

Albert Szent-Györgyi was a man of success. Nobel Prize winner George Wald wrote about him recently: "Szent-Györgyi with his life work deserved three Nobel prizes". I suppose there have been very few scientists in this century about whom this could be said. But whoever thinks that he had an easy life is making a great mistake. It was no easy at all. From his youth he had to cope with more and more problems. He was really lucky to survive two World Wars. As a beginner he had serious financial difficulties after graduating from the University, until he became a research worker with a subject of his own in the laboratory of the famous Professor Hopkins. When he was invited to the University of Szeged this facilitated him in finding coworkers and broadening his research field. Financial conditions, however, were not provided and he had to fight for funds. His political view was opposed to the class in power and he was always envied and criticised by many.

Albert Szent-Györgyi was an extremely inquisitive man. He was interested in a great many things outside the scope of his research field, such as literature, music and the fine arts as well as social and political problems. I shall not go into details, since his works and writings are accessible. But in one context I feel it important to recall a memory, which may have a beneficial impact on the attitude of our young people.

As the Rector of the University of Szeged during the 2nd World War, he tried to introduce a new mentality but very soon after he was forced into illegality. In the years after the liberation of Hungary by the Soviets he invested vast energy in research management and the reorganization of the Hungarian Academy of Sciences. Disillusioned by the policy of the personal cult his fate became the bitter life of immigrants. We were happy to welcome him in our country again at the age of 80. Then the whole country could witness his wisdom. He had a really hard life but nothing could prevent from reaching the peaks of science. The message of his teaching — "Only he who fights for the truth again and again, is able to create" — will always be remembered.



Address of Brunó F. Straub, Vice President of the Hungarian Academy of Sciences

5.

PROFESSOR ENDRE SOMOGYI

On Behalf of Hungarian Medical Universities and Institutions

Magnifice Rector!

Honoured Guests!

The Medical Universities of Debrecen and Pécs have conferred on me the honour of greeting you on the occasion of this special event. In the history of an Institution there is hardly any occasion other than renaming where there is time to look back to the past but also for to the future. It means a conscious acceptance of life because it means an identity with both the veracities and errors of the name-giver. In this context renaming is an intention to regard the name-giver as an example, and his memory a spiritual inspiration which remains living and topical. I suppose the major objectives in choosing the name of Albert Szent-Györgyi are not only a tribute to the past.

The name and university background of the Nobel prize winning scientist Albert Szent-Györgyi further enhance the scientific and public respect of the University on a national and an international scale alike. I believe that Universal research is the symbol of the near future and progress of the University. Training, medicine and scientific research are the catalysts for the challenges of the 21st century. In one of his works Albert Szent-Györgyi wrote the following: "There might be differences between the two worlds, namely prescientific and scientific eras. It is, however, undeniable that the world of science is also the world of peace."

This was the guiding principle of the throbbing, ever passionate life of Albert Szent-Györgyi. It is also witnessed by his own thoughts when he declares: "Looking back on my past I see that I have been seeking peace during all my eventful life." His scientific and public projects thus always merged.

Albert Szent-Györgyi's Szeged citizenship also involves his nationality and internationality. It also involves the fact that he used to be a professor of the Péter Pázmány University of Sciences, and at whatever stage he could he co-operated with Hungarian medical universities. This attitude led later to the pressure-born idea of establishing a laboratory free of walls, which became one of the greatest spiritual ventures of the 20th century and a means of cooperation between top-ranking research institutions.

Some of us present in this room might consider ourselves lucky to have had the possibility to become acquainted with Albert Szent-Györgyi not only through stories and writings but personally. For some of us he was our teacher or colleague, for others an intellectual partner as well. It is foreseeable that some features of his portrait will change along with the historical perspectives, certain elements will be stressed and others ousted. I assume, however, that the paramount impact of the personal contact, the indirect memories mean an inner strength which might initiate expected social and scientific changes.

I do not intend to talk about the scientific results of Albert Szent-Györgyi, since numerous books and papers have been published on them. I would rather say, that choosing a name puts one under obligation and we respect the University for this decision: it is a privilege for the Hungarian medical community to live with the memories of Albert Szent-Györgyi. We hope the idea of a laboratory without walls will further connections not only at international level but also between Hungarian medical universities.

With these thoughts I wish for successful work worthy of the name-giver in training, medicine and scientific research on behalf of the Medical Universities of Debrecen, Pécs, the Institute for Medical Postgradual Training and my own Institute the Semmelweis Medical University of Budapest.

Finally let me present to you the respectful message of the Council of my University.

6.

PROFESSOR KLAUS KÜHL

On behalf of Medical Universities abroad

Hochverehrter Herr Staatspräsident!
Hochverehrter Herr Gesundheitsminister!
Hochverehrte Vertreter der gesellschaftlichen und staatlichen Einrichtungen!
Magnifizenzen! Spectabilitäten!
Meine sehr verehrten Damen und Herren!

Es its eine grosse Auszeichnung, dass ich als Vertreter der Ernst-Moritz-Arndt-Universität Greifswald Gelegenheit habe, mich für die Einladung anlässlich der feierlichen Namensverleihung Ihrer Universität im Namen der anwesenden Teilnehmer der wissenschaftlichen Einrichtungen des Auslands recht herzlich zu bedanken.

Ich bedanke mich damit im Namen des Rektors der Medizinischen Akademie Odessa sowie im Namen der Rektoren der Universitäten Olomouce, Ulm und Greifswald.

Mit Freude sind wir Ihrer Einladung gefolgt, um Ihnen zu der feierlichen Namensverleihung unsere Glückwünsche zu überbringen. Als Vertreter der 531 Jahre alten Ernst-Moritz-Arndt-Universität Greifswald bin ich stolz darauf, dass unsere beiden Universitäten seit 1971 durch den somit ältesten Freundschaftsvertrag verbunden sind.

Der ehrenvolle Name des Biochemikers Albert Szent-Györgyi, dem für seine Arbeiten über biologische Verbrennungsprozesse, 1937 der Nobelpreis für Medizin verliehen wurde, ist Würdigung und Verpflichtung zugleich. Dieser Name soll uns Richtschnur für das Erbringen weiterer hoher Leistungen auf dem Gebiet der medizinischen Lehre, der medizinischen Forschung und der medizinischen Betreuung in einer Welt des Friedens sein.

Magnifizenz, werte Anwesende, mögen unsere freundschaftlichen Verbindungen ganz im Sinne des Nobelpreisträgers Szent-Györgyi dazu beitragen, die medizinische Wissenschaft voranzutreiben, um immer bessere diagnostische und therapeutische Verfahren für eine immer besser werdende Betreuung unserer Patienten zu entwickeln.

Mögen unsere gemeinsamen Bemühungen dazu beitragen, an unseren hohen Schulen Studenten auszubilden, die wir — mit einem soliden Fachwissen und praktischen Fähigkeiten ausgestattet — in ihr späteres Berufsleben als Ärzte, als Wissenschaftler oder als Hochschullehrer entlassen können.

Zur Lösung dieser anspruchsvollen Aufgaben wünsche ich Ihnen, Magnifizenz Prof. Szilárd und Ihren Mitarbeitern Gesundheit und Schaffenskraft.

7.

PROFESSOR JÁNOS SZILÁRD

Presentation of the "Albert Szent-Györgyi Commemorative Medal" to Professor Ilona Banga

The Council of the Medical University of Szeged at its 3rd regular meeting founded an "Albert Szent-Györgyi Commemorative Medal" to be presented for the best research results achieved.

According to the rules of presentation "the Council of the Albert Szent-Györgyi Medical University to commemorate the Nobel prize winning Professor decided on the foundation of the Albert Szent-Györgyi Medal to be presented in acknowledgement of outstanding scientific work done for the benefit of the health of mankind and for better cooperation and understanding.

Proposals for the decoration can be made every other year. Persons recommended can be Hungarian and foreign alike, who have achieved outstanding results in the field of medical science and promoted better human understanding".

Our University wishes to present the first medal to professor Ilona Banga.

Professor Ilona Banga (wife of Professor József Baló), doctor of biological sciences, studied at the Universities of Szeged and Vienna. She obtained her doctor's degree in 1929, then conducted research in enzymology at the Department of Medical Chemistry and physiological studies with professor Verzár at the Department of Physiology of Debrecen.

Ilona Banga was recommended to Albert Szent-Györgyi — with whom she worked for 17 years — by her professors at the beginning of the 30's, the first pioneering era of the Department of Medical Chemistry of Szeged Medical University. The main research project at this time was carbohydrate metabolism. The second pioneering era of the Department headed by Albert Szent-Györgyi was between 1940—44. The common research work of Albert Szent-Györgyi and Ilona Banga resulted in the discovery of actin and its isolation from actomyosin. The isolation and characterization of actin are due to the merits of Professor Straub. As to the significance of these research results they would have deserved another Nobel prize if the years of the Second World War had not prevented their publication abroad. When Albert Szent-Györgyi and his male colleagues had to escape to avoid drafting and Nazi persecution, Ilona Banga remained at the Department and thanks to her courage the Deparment of Medical Chemistry was the only institution of the University where all the equipment and facilities were preserved, including the entire stock of the Klebesberg Library. During the years following the liberation of Hungary by the Soviets, Ilona Banga worked in Budapest. Arteriosclerosis research was her main field of interest and she discovered and isolated elastase, an enzyme dissolving the elastic fibers in walls of blood vessels. For the results of this research project she and her husband József

Baló were awarded the Kossuth Prize in 1955. In the ensuing years she studied connective tissue of blood vessel walls and its changes during the aging process. Her books aroused great interest not only in Hungary but abroad as well.

With these words I wish to present the Albert Szent-Györgyi Commemorative Medal to Professor Ilona Banga with the highest respect and appreciation.

8.

Conferment of the degree of doctor "Honoris causa"

PROFESSOR JÁNOS SZILÁRD, Rector of Albert Szent-Györgyi Medical University

We wish to continue this renaming celebration — following the old traditions of our University — by conferring degrees of doctor "honoris causa" on four outstanding scientists from abroad.

I sincerely welcome in our town and University

Professor SERGE BONFILS
Professor EGON DICZFALUSY
Professor HELMUT KALA
Professor JOACHIM WOLFF

I am happy to inform you that the Council of the Szeged University of Medical Sciences at its meetings held on June 20, 1986, December 19, 1986 and on June 19, 1987, respectively, decided to confer the degree of doctor "honoris causa" for your internationally acknowledged results in the medical and pharmaceutical sciences and for furthering the contacts between our Universities.

Now I invite the Deans of our University to outline the main landmarks in the career of the candidates for the degree of Doctor "honoris causa".

PROFESSOR GYULA TELEGDY, Dean of the Medical Faculty at Albert Szent-Györgyi Medical University.

Professor SERGE BONFILS has been working at the Faculty of Medicine at the University of Paris since 1945. In 1970 he was appointed head of the Internal Department of the Hospital Bichat. His predecessor and teacher at this department was Professor Lambling, who is regarded as the greatest living French gastroenterologist.

Professor SERGE BONFILS is the leading personality in French Gastroenterology. Until 1984, besides running the Department of Internal Diseases, which focuses particularly on gastroenterologic problems, he also performed the duties of director of the INSERM (U.10) Research Institute. Since 1984 he has continued in charge of the clinic, but as the leader of his research team he participates in the work of the Research Institute, now functioning under the leadership of one of the members of the school he has created. In 1983 he was the president of the French Gastroenterologic Society. At present he is the active vice-president of the gastroenterologic World Organization (OMGE). Besides the French Gastroenterologic Society, gastroenterologic societies abroad (e.g. in the USA and England) have also elected him as a member. He was elected honorary member of the

Candidates for the degree of doctor "Honoris causa" and representatives of universities.

Hungarian Gastroenterologic Society in 1985. His scientific work is marked by a great number of books, publications and lectures.

Professor BONFILS's connection with Hungarian internists, including gastroenterologists, dates back more than twenty years. He has made it possible for four internal specialists from our University to take part in one-year fellowships in France. With the support of the Cercle André Lambling, founded in honour of his predecessor, two clinicians from the socialist countries, both from Szeged, have so far been invited to Paris to become acquainted with the achievements of French culture.

Professor SERGE BONFILS is a clinician and researcher of international repute. He has visited Hungary several times and has been of great help to our University in the course of preparatory work for scholarships and scientific co-operation by promoting relations between researchers from Szeged and French institutes. Apart from clinicians, organic chemists participating in peptide-research have benefited from his support.

This conferment of the title of Doctor "Honoris Causa" on Professor BONFILS is a symbol of the warm scientific relations between Hungary and France. The international prestige of our university can only be increased by this award to Professor BONFILS.

Professor EGON DICZFALUSY was born in Miskolc on 19th September, 1920. He was a student at our university from 1938, and graduated here "summa cum laude" in 1944. While a student, he worked, as an assistant at the Instute of Pathology and Bacteriology, together with Professor Ivanovics, from 1942 to 1945. He then joined the staff of the Institute of Biochemistry. He started his research work in Szeged and his first results were published here. In 1946 he moved to Sweden, where he continued his work at the Karolinska University in Stockholm. He was director of the Reproductive Endocrinological Research Institute of the Swedish Medical Research Council from 1967 to 1981, and in 1981 he was appointed director of the Department of Reproductive Endocrinology of the Karolinska Institute. Furthermore, he is director of the Research Institute of the World Health Organization in Stockholm and a leading consultant of the Human Reproduction Program of the World Health Organization.

The main subject of his research work for many years has been human reproduction. The term "foetoplacental unit" is associated with his name, and his investigations have provided basic knowledge about the hormonal function of the placenta. During the past 20 years he has mainly been studying the contraceptive aspects of human reproduction. His achievements have been published in more than 500 papers. The books written or edited by Professor DICZFALUSY number about 20.

Professor DICZFALUSY is an honorary member of 15 international medical societies, including the Hungarian Endocrinological and Metabolic Society and the Society of Hungarian Gynecologists. He has been awarded several high-ranking medical medals (the Ruth Gray Medal, the Medal of the Barren Foundation, the Sir Henry Dale Commemorative Medal, and the Commemorative Medal of the Academy of Paris). He has been or is a member of the editorial boards of the 10 most important endocrinological journals.

He has always maintained close contacts with Hungarian medicine, and with our university in particular. He played a great role in the selection of the Department of Gynecology and Obstetrics, University Medical School, Szeged as a World Health Organization Clinical Research Center in 1972. He has been an active supporter of

the collaboration between this center and the World Health Organization ever since. This has meant considerable financial support, besides the scientific achievements and the fellowships for several research workers from this Department. He has been to Szeged several times as a representative of the World Health Organization. He has made it possible for more than ten Hungarian researchers to spend a one- or two-year fellowship at his institute, the good results of which are reflected by nearly 20 joint publications. Several researchers from our university have also spent long periods at the Institute of Professor DICZFALUSY or have paid him short visits in Stockholm.

By virtue of his world-famous research work, his close scientific connections with Hungary and Szeged in particular, and his constant good will and readiness to help, Professor DICZFALUSY, who gained his medical degree at our university, is fully worthy of the degree of doctor "Honoris Causa", which is conferred upon him by this university. This award to Professor DICZFALUSY is a further sign of the continuation of the friendly and fruitful Swedish-Hungarian relations, and it greatly adds to the prestige of our university.

Professor JOACHIM WOLFF was born on 25th March, 1935 in Berlin. He graduated from the Medical University of Berlin in 1960. From 1961 to 1971 he worked as researcher and lecturer at the Institute of Anatomy. He was then invited to Basel, as a guest researcher by the firm Sandoz, where he worked for one year. Between 1971 and 1980 he was head of the Neuroanatomy Unit of the Max-Planck Institute, Göttingen. Since 1980 he has been director of the Anatomy Institute and Developmental Neurobiological Centre of Göttingen University. He has been a guest professor in Berlin, Würzburg, Regensburg, Heidelberg, Basel and Sydney. For his outstanding achievements in the field of neuroscience, he was requested to join the Wissenschaftskollege zu Berlin in West-Berlin for a year.

Professor WOLFF's scientific activity, the exploration of the vascularization developmental mechanism of the cortex and the plasticity of the central and peripheral nervous systems, with special regard to his scientific work in the field of the induction of neuronal plasticity without lesion, has won international appreciation. The results of his research work have been published in a great many books and in more than 200 scientific papers. He is internationally recognized for his scientific achievements, and received an honorary doctorate from the University of Göteborg in 1978.

He is a member of many scientific societies, for instance the International Brain Research Organization, the European Neuroscience Association, the International Society for Developmental Neuroscience, the International Society for Stereology, the Anatomische Gesellschaft, and the Deutsche Naturforscher und Arzt-Gesellschaft.

Professor WOLFF is always willing to work together with Hungarian researchers. His connections with our country and particularly with Szeged date back more than a decade. During that time he has received 18 Hungarian researchers, who have spent altogether 16 years at his institute.

On this basis, and in the knowledge of Professor WOLFF's affection for Hungary, we can be sure that, by conferring on him the degree of doctor "Honoris Causa", we are strengthening the long-established Hungarian — West-German connections. This award further enhances the reputation of our university.

On the basis of all that has been put forward. I, Gyula Telegdy, university professor and Dean of the Medical Faculty, confer the degree of Doctor "honoris causa" upon

and confer on you all the rights due to honorary doctors according to the rules and customs of our university.

I wish that you, in the possession of the highest decoration our university can give, have the strength to strive towards the enrichment of your research field and the successful training of the next scientific generation for the benefit of science and mankind.

PROFESSOR BÉLA SELMECZI, Dean of the Faculty of Pharmacy at the Albert Szent-Györgyi Medical University

Professor Dr. HELMUT KALA was born on 18 th January, 1926, in Kreisfeld. After receiving his degree in pharmaceutics in 1953, he worked as a research assistant at the Pharmaceutical Institute of the Martin Luther University in Halle. Here he received his university doctorate, after which he was appointed first research assistant and was invited to lecture on drug analysis and drug technology. In 1963 he became a lecturer, in 1964 associate professor and in 1967 full professor. Two years later he was appointed head of the Drug Technology Institute of the Pharmaceutical Faculty.

As a distinguished scientist in the field of pharmaceutics, in 1971 he received the title of Academic Doctor of Sciences.

Professor KALA's scientific work has always been characterized by co-operation with the pharmaceutical industry. In recognition of his scientific research, he has been awarded the Research Prize of the Martin Luther University three times. In 1981 he received the Thomasius Medal.

Four of his students have been appointed university professors. He has so far produced over 150 publications and 15 patents. He has participated in numerous conferences in his home country and abroad, ranging from Paris to Cairo, where he has reported on pharmaceutist training in the GDR and on his own world-famous research.

Professor KALA has always placed special emphasis on international co-operation. Thus, he has carried on intensive and fruitful co-operation with the Drug Technology Institute in Szeged for 20 years. He and his colleagues spend one month in Szeged every year, exchanging working methods and lecturing. 15 publications have so far resulted from this co-operation. The staff of the Szeged Drug Technology Institute have all visited Professor KALA's institute on study tours or to exchange working methods on several occasions.

Besides his outstanding educational work and scientific research, Professor KALA has always taken an active part in community and civic work. While still an associate professor, Professor KALA was elected to the Pharmaceutical Scientific Committee, where he was President of the Training and Educational Board for 10 years. For almost 20 years he worked as deputy director of the educational section of the Pharmaceutical Department. He has been a member of the Presidium of the Drug Technology Panel of the Pharmaceutical Association of the GDR for 10 years. He is one of the founders of the Special Drug Technology Committee of the Berlin Medical Graduate Academy. In this position he has worked actively in the field of training specialist pharmacists. For 10 years he was president of the

Revisional Committee of the Pharmaceutical Association of the GDR. In 1971 the Ministry of Health of the GDR awarded him the title of pharmaceutical chief counsellor.

In honour of his achievements, he has received numerous awards, among them the Döbereiner Award, the Hufeland Silver Award, the Carl-Wilhelm-Scheele Prize and the golden Award for Service to Public Health and Social Work.

Professor KALA's scientific accomplishments are known and recognized throughout the world. His professional and personal relationships in Hungary, and especially Szeged, have proved fruitful and permanent, and he is undoubtedly worthy of the conferment of the degree of doctor "Honoris Causa" by our university.

On the basis of all that has been put forward, I, Béla Selmeczi university professor, Dean of the Faculty of Pharmacy at the Albert Szent-Györgyi Medical Univesity, confer the degree of Doctor "Honoris causa" upon

Professor HELMUT KALA

and confer on him with all the rights due to honorary doctors according to the rules and customs of our University. I wish that you, in the possession of the highest decoration our University can give, have the strength to strive towards the enrichment of you scientific field and the successful training of the next generation for the benefit of science and mankind.

After the conferment Professor János Szilárd Rector of the Albert Szent-Györgyi Medical University greeted the new honorary doctors of the University.

9.

PROFESSOR EGON DICZFALUSY

On Behalf of the Newly Accepted Honorary Doctors of the University

Magnifice Rector, Arade Medlemmar is Universitetsstyrelsen,
Mina Damer ach Herrar! Honoured University Council!
Ladies and Gentlemen!

I have been honoured with the duty of expressing our gratitude for this high decoration on behalf of all four of us. Not long ago, about 200 years before, during the French Revolution, Jean Baptiste Coffinhal backed up by the Convent signed the death penalty of the famous chemist Antoine Lavoisier in 1794, with the following remark: "La république n'a pas besoin de savants" — "The republic has no need for scientists". In the same year Georg Christoph Lichtenberg drew the following character of one of his professor colleagues in Königsberg: "Der Mensch hatte so viel Verstand, dass er fast zu nichts mehr in der Welt zu gebrauchen war" — "Man is so clever that he is of no further use at all any more."

Much water has flown under the bridges since then, and the modern society of nowadays has recognized the need for a world with scientists after all, and scientists have also realized that modern science has essential social dimensions. Forty years ago on 10th December I heard a Swedish statement on scientific research, at a Nobel Prize awarding ceremony that I have not been able to forget ever since "Förskning ar det lidelse fulla sökanaet efter del liderlse fria sanningen" — "Research is a zealous search after a stoical truth". In think that modern medical research has an even higher level of ambition than that, since over and above the search for truth, the target is to relieve human suffering and to improve the quality of human existence.

In this context, we, the first doctors "honoris causa" of the Albert Szent-Györgyi University, wish great success in this endeavour. We hope we have many years of further fruitful cooperation ahaead of us for a better future.

Magnifice Rector, honourable University Council, Ladies and Gentlemen. Now I have to meet a honouring obligation. In a few hours, this afternoon, on the Anniversary of the birth of Alfred Nobel, the Nobel prize winners of 1987 will take their prizes from the hands of King Charles Gustav. That is why Professor Samuelsson Bangts, Rector of the Karolinska Institute — who is himself a Nobel Prize winner — entrusted me to represent him and the Karolinska Institute, and pass on the warmest greetings of the Institute as well as those of the Nobel Committee and their best wishes to the future activities of the Albert Szent-Györgyi University*.

* Translated from Hungarian

10.

PROFESSOR JÁNOS SZILÁRD

Closing Speech

I wish to express my grateful thanks to Professor Diczfalusy for his most kind words and special thanks for the message of Professor Samuelsson. I believe that contact between the four new Doctors "Honoris causa" and our University and Hungarian medical science may be a modest acknowledgement of their activities, but it may be a little more than a modest sign of our University's intention to act in the spirit and principle of Albert Szent-Györgyi as already acknowledged by the Nobel prize Committee 50 years ago.

As we approach the end of this ceremory, allow me to thank our doctors "honoris causa" of former years: Professors Paul Bacsich, László Lajtha, Otto Prokop, G. Wooler, David de Wied, as well as the Heads of our Fellow Universities, Professor A. Rousi Rector of the Turku University, Professor N. Kamp President of Göttingen University who due to other obligations were unable to be present but sent their best wishes by letter. These greetings and attentions as well as the response to our renaming in geographically distant countries, indicate that this day and event is an important contribution in the enhancing of our University's reputation and also in strengthening and extending our scientific contacts on Hungarian and international levels alike.

As we arrive at the end of our renaming celebration I wish to thank Károly Németh as well as all of those who have graced our celebration with your presence.

Opening of the banquet. Professor Gyula Telegdy dean of the Medical faculty, Mrs. Albert Szent-Györgyi, János Szilárd, Rector, Károly Németh President of the Presidium, Professor Ilona Banga, Professor Béla Selmeczi, Dean of Pharmacological Faculty.

II. UNVEILING OF THE BUST OF ALBERT SZENT-GYÖRGYI IN THE SZEGED PANTHEON IN DOM SQUARE

11th December, 1987,
9.30 a. m.

1.

MRS. JÓZSEF MÜLLER

Inauguration Address

Honoured Guests!

It is 50 years now that on 1st December, 1937, the Nobel Prize winning scientist, Albert Szent-Györgyi, became a freeman of the city upon the decision of a special assembly of the Szeged City Council. And now, by inaugurating his bust here on the wall of the national pantheon in Szeged, among the great figures of Hungarian history, science and culture, we wish to manifest our respect and gratitude towards this outstanding and fine man. Szeged is the only town in our country privileged to have a Nobel prize winning citizen: a scientist, who achieved the results of the research for which he was decorated here in this town using in his work a special product of this region, the green pepper. Szeged certainly has much to be thankful for to Albert Szent-Györgyi. The town became known throughout the world overnight, and also the fact that this important scientific work was being conducted here in Szeged to the benefit and in the interest of mankind, as is still the case. I suppose it is justified that we Szeged citizens — knowing that we can thank the genius of this scientist for these outstanding research results — are especially proud of Albert Szent-Györgyi and we regard his activities in our town as an important landmark in the history of science and education.

"I went to work in Szeged" he wrote once "The conditions were provided: co-workers, laboratories. All I needed was peace and quiet, and I got it". When in October 1973 he returned, unfortunately for the last time, and his former university conferred the degree of doctor "Honoris causa" on him, he expressed his attachment to Szeged — his home town for 15 years — in the following words: "I was happy to come home again, to see the places where I used to live and work. I wanted to meet old colleagues and also to see what has become of my former students. My homecoming had, however, another aim, namely to recharge the "batteries" of my emotions. I wish to strengthen the links attaching me to Hungary and Szeged University." This feeling was mutual. The question may arise in us: What is it that maintains this sincere interest? It is surely not mere local-patriotism or pride, that this great figure of universal science was connected with our town. It is much more, I think: the personal magnetism of an extremely colourful, renaissance-type personality and a spirit with universal thoughts and problems. His extraordinary popularity can be attributed to his humanistic attitude, and the purity and wisdom of his spirit. He declared that science should serve man and mankind. We all know that he was led by this principle throughout his long and rich life. This is an attitude which can be called humanistic but it can be also regarded as a policy. When in 1937 he was on his way to Sweden to receive the Nobel prize he said in an interview to Népszava (Voice of the People): "Men of science are most worried

about peace throughout the world. All our efforts will be in vain if our discoveries are being used as tools of destruction, and fruit of our peaceful work will be diminished by a world war. The political tension nowadays is frightening, though there would be enough bread and space for everyone, if we could properly accept each other."

I think that we who pay homage to him in front of his bust know that Albert Szent-Györgyi not only talked about his principles but was ready to act for his country and people if needed. Therefore, we know we have an example to follow. I hope this bust will make all of us remember it. When we pass it in our everyday life, we should remember that we are indebted to him, to this country and to mankind. And we should also keep in mind that our University bears his name from now on.

Bust of Albert Szent-Györgyi carved by György Kalmár sculptor

2.

PROFESSOR FERENC GUBA

Fellows' Reminiscence

We are gathered here to raise a monument to Albert Szent-Györgyi whose name our university bears, close to the place where he worked so successfully.

The magnificence and warmth of our celebration is increased by the presence of the members of Szent-Györgyi family, besides the leaders, lecturers and students of the University and Szeged citizens devoted to the Professor. Raising the bust at this very place has a double significance. The arcades of Dom square buildings provide a place for the pantheon of Hungarian intellectuals, where monuments remind us of the greatest Hungarians who were pioneers of culture and eternal human progress: founders of Universities, writers, poets, scientists. Albert Szent-Györgyi the Nobel prize winning biochemist is worthy of his place among the great citizens of our country proving that our town highly respects this creative man.

This pantheon serves as a pattern especially to young people. Whenever school children walk around under the arcades and listen to their teachers' enthusiastic words raptly, we can be sure, that our celebration today will contribute to development in our country. The actual place where the bust has been put up is associated with this thought, that is the entrance to the Department of Medical Chemistry. For many years professor Szent-Györgyi went through this entrance to his daily work. Lately, we have been talking a lot about his work, and especially about its scientific significance.

Now I would rather speak about him, the affectionate friend and teacher of the young. His informal and charismatic personality had always had a great influence on the young. From his numerous exemplary activities, we have also inherited his principle: that our future is carried on by the young. To teach and educate is a sacred act, therefore it should be pursued like activities leading to factual results. He had humanistic principles in training, and he liked young people sound in body and mind around himself. When raising this bust to professor Szent-Györgyi we put ourselves on the side of the humanist he represented not only in words but also in his actions.

Thank is due to Márton Kalmár sculptor for reflecting in the bust all the spirit and pure humanistic strength characteristic of Albert Szent-Györgyi. May this bust enrich the Szeged pantheon of the greatest Hungarians and demonstrate to the present and future generations that the progress of a nation is based on the esteem of human qualities and creative work.

Inauguration of the bust of Albert Szent-Györgyi in the Szeged Pantheon (Professor András Szent-Györgyi and Mrs. Szent-Györgyi on the right-hand side).

III. SCIENTIFIC SESSION — LECTURES OF THE DOCTORS "HONORIS CAUSA"

At the Medical Education Center of the Albert Szent-Györgyi Medical University

11th December, 1987
10.00 a.m.

1.

Hormone secreting tumors of the pancreas: Some insights into their clinical and fundamental interest

PROFESSOR S. BONFILS
Faculté de Médecine X. Bichat et Hôpital Bichat — Paris

Clinical and fundamental research have been progressing simultaneously in the field of hormone secreting tumors. Concerning fundamental research the interest of human endocrine tumors was originally recognized for pituitary and adrenals. For non-steroid hormones, the importance of clinical studies was later on disclosed with improvement of diagnosis of insulinoma and serotonin-secreting tumors. As far as pancreatic tumors are concerned, gastrinomas with the Zollinger-Ellison syndrome (ZES) as clinical presentation were as early as 1968 exceptional material for basic research in molecular forms of gastrin and in gastric secretion mechanism.

Gastrinoma or Zollinger-Ellison syndrome (ZES): an elective model (1)

Clinically ZES (1) is expressed in 85% of cases as a very common disease, peptic ulcer. 1/1000 is the approximative prevalence of ZES in patients with duodenal ulcer. Diagnosis of ZES is now more easily obtained with better clinical recognition, the use of provocative tests (secretin test) and progresses in imagery (CT scan, arteriography). Besides therapy with specific drugs, mostly gastric antisecretory substances (H2-blockers; benzimidazole derivatives) (2), attempts to excise the tumoral process is a major therapeutic orientation.

Hepatic metastases (HM) are often the only evidence of malignancy in the ZES. In a personal series (3) of 144 consecutive ZES cases with a mean follow-up period of 50 months, prevalence of HM was 25%. Preoperative imagery gave the final diagnosis of HM in only half of the cases. In the other half of the cases, diagnosis was obtained by systematic laparotomy.

HM were responsible for 50% of the 46 non-operative deaths. At 5 years, 5 of 29 patients (17%) of the synchronous HM group were still alive vs 65% for the entire population.

Results of chemotherapy for HM in Zollinger-Ellison syndrome was recently analyzed in the largest published series resulting from a multicentric study (4). 45 ZES patients were treated by Streptozotocin (STZ) for HM in 12 European, American or Australian centers.

In the majority of the cases, treatment modalities were those proposed by Moertel (5). Actually, total STZ dosage was highly variable (median value : 10 g/sqm, extremes : 2.5—87). Route of administration was intravenous, into the hepatic artery or both. 5 FU was associated in 28 patients, dauxorubicin in 9 and tubercidin in 4.

Therapeutic effect was appreciated according to OMS criteria, HM size being measured by the best imaging technique for each patient (ultrasonography, CT scan, arteriography). Objective response was noted in 42% of the cases : 9 complete remissions, 10 regressions with a latence of 17 weeks in mean. Stability was noted and tumor progression in 13.

Toxicity was limited to nausea and/or vomiting (84%) and to transient mild proteinuria or tubulopathy (30%).

In conclusion, except insulinoma, ZES is the most frequent presentation of pancreatic tumors with hormone secretion. Thus diagnosis is often discussed in the presence of ulcer disease and/or steatorrhea. Diagnosis is better suggested by routine gastric secretion studies than gastrin measurement, but a provocation test with secretin infusion and simultaneous measurement of serum gastrin and gastric acidity is the best tool for obtaining diagnosis certainty. Prognosis has been largely improved by the development of 1) gastric antisecretory drugs for suppressing the harmful situation due to gastric hypersecretion, 2) Chemotherapy of liver metastases, 3) More ambitious tumor surgery in well-defined conditions.

As far as basic research is concerned gastrinomas are a source of precious material. In this tissue gastrin secretion is very intense and obviously represents the major (if not unique) activity of the tumor. Thus, biological studies can be carried out either on dispersed tumoral cells from fragment surgically collected from pancreatic and metastatic gastrinoma or from cultures.

Initial by work Lichtenberger et al (6) did not succeed in obtaining either a survival time of the primary culture over 6 weeks or an adequate responsiveness to hormonal stimulants.

According to Ellison et al. (7), acute gastrinoma cell dispersion experiments allow to measure gastrin concentration in the medium and the pellet in the basal state and after stimulation but with a rapid fading in the release.

In our group (8), starting from tissues of 5 patients (4 pancreas and one liver metastasis) successful cultures were obtained with internative passages and a survival time of gastrin secreting endocrine cells presently over 5 months. Responsiveness of the model to stimulants (DB cAMP, Ca^{++}, bombesin, carbachol, secretin, phorbol ester) and to inhibitors (somatostatin) was successfully tested with excellent reproducibility and no time-related fading. Immunochemical (immunogold) evidence was obtained in many cases for the structural identities of the cultured cells with the initial sampling concerning morphology and hormone secretion. Some features of the cell structure exhibit modification, however particularly in granule density and shape.

Multiple-hormone secreting tumors and MEN I (9,10)

Ectopic hormone production is the phenomenon by which certain neoplasms produce hormones not usually produced in significant amount by tissues from which neoplasms arise. Pancreatic gastrinoma gives rise to ectopic hormone production since gastrin is not normally secreted by the endocrine pancreatic tissue. In this condition multiple hormone production (10) is not uncommon: the most frequently observed are VIP (5—10%), glucagon (10—20%), somatostatin (10—20%), PP (15—20%), insulin (20—30%), ACTH (10—30%). For fundamental research, ectopic hormone-producing tumors provide a potential model for investigating the control of gene expression, especially the differences between ectopic hormone and entopic hormone production.

MEN I fundamentally raises the same kind of problems (9). Prevalence in ZES is over 25%. Parathyroid involvement is the most frequent (82% of ZES with MEN I). The high rate of relapse after parathyroidectomy (in contrast to primary adenoma) implies the presence of a systemic stimulatory factor in keeping with the diffuse pancreatic lesions constantly observed in ZES with MEN I (at variance with sporadic ZES).

Vipoma or Verner-Morrisson Syndrome: cAMP activation and relevant symptoms (11, 12, 13).

They are rare tumors and the published cases of the largest series involve no more than 200 patients. Neuroendocrine tumors that elaborate vasoactive intestinal polypeptide (VIP) in excess are found in the pancreas (90%) and in neural tissue (neuroblastomas, ganglioblastomas) of the autonomic nervous system (10%) including the adrenal medulla. Single primary neoplasms constitute 80% of the pancreatic tumors, but hepatic metastases do occur in about one-half of them; islet cell hyperplasia is present in 10 to 20% of the patients. There is good evidence that the cellular source of VIP may be the neural cells within the pancreas and/or the endocrine cells of the islets (12). Thus there is a dual role for VIP, neural modulation and endocrine. The potent endocrine function of vipomas stimulates cyclic AMP in the exocrine cells of the gut to produce a massive secretion of water and electrolytes into the small intestine that overwhelmes the normal absorptive capacity of the colon. Because VIP is a molecular member of the secretin-glucagon family, it has endocrine functions similar to secretin, such as increased pancreatic bicarbonate excretion and gastric acid inhibition, as well as a glucagon-like action of abnormal glucose tolerance. There is also a vasomotor action of VIP that causes vasodilatation.

Thus, the most prominent feature clinically (11,13) is the profuse watery diarrhea in volumes often exceeding three liters per day; it may be explosive, episodic and may occur even during fasting. The resulting dehydration and hypokalemia produce weakness that may progress to hypotension, compounded also by the accompanying vasodilatation. Either hypochlorhydria or achlorhydria is frequently observed in spite of normal parietal cells being present in the stomach. Distended and enlarged gallbladders have been observed. The lethargy seen in approximately 50% of these patients may be due in part to the hypercalcemia. Increased plasma concentration of VIP is a major argument for diagnosis.

Vipoma is a model for intestinal absorption and secretion studies (14); an increase in adenylate cyclase activity of the enterocytes may be main explanation for diarrhea, although other diarrheogenic hormones (PP, PG, calcitonin) might be also secreted by the tumor. This biological responsiveness of enterocytes to VIP was proposed as a basis for a biossay (13). Paradoxical observation of cAMP stimulation of the gastric musoca with acid secretion inhibition is not yet fully understood.

Somatostatinoma: a suggestive model for the therapeutic use of somatostain

The syndrome produced by excessive elaboration of somatostatin has been designated the inhibitory syndrome because of its physiologic and pharmacologic effects of inhibition of the release of insulin, glucagon, gastrin, and cholecystokinin (16). Its inhibitory actions on secretin, vasoactive intestinal polypeptide, motilin, thyroid-stimulating hormone and growth hormone are not clinically apparent in the syndrome. The clinical findings associated with the presence of a somatostatinoma include diabetes, cholecytolithiasis, steatorrhea, indigestion, hypochlorhydria and,

occasionally, anemia (11,17). Less than 30 patients have been reported to have somatostatinomas.

Here again, pathophysiological studies could be based on cell biology concepts (18). Somatostatin receptors are diffused in the body and receptor studies, even on isolated cells, could lead to a better understanding of the biochemical background (19,20). However adaptation to a greatly excessive release of somatostatin is apparently good for a long period of time without endangering life.

The use of somatostatin in the management of hormone-secreting tumors, particularly those located in the digestive tract, was proposed more than 10 years ago. The inhibitory effects of somatostatin on the secretion of most gut hormones brought high hopes of a beneficial effect of chronic therapy with this type of patients. Only recently has the new molecular form, SMS 201-995 (Sandostatin), allowed the overcoming of problems in the short duration of action natural somatostatins and particularly the requirement of administration by infusion (21, 22, 23).

In ZES, numerous publications evidenced ability of SMS to decrease serum gastrin and acid secretion for several hours after a single subcutaneous injection; only recently its practical usefulness in a management scheme, applied over months or years, has been tested by our group. Five patients were to treated during 9 to 12 months. Basal acid output presented a sustained decrease in 4 out of 5 cases, allowing ranitidine discontinuation. The serum gastrin level was affected to a greater extent showing a mean 87% decrease throughout the treatment period. Tolerance of SMS was excellent and we concluded that antitrophic and antigastrin properties of SMS could improve the therapeutic efficacy in long-term management of ZES (22).

In VIPoma patients the beneficial action of SMS was readily shown. The diminution in the elevated circulation of VIP was probably not enough to explain the outstanding clinical improvement. A direct inhibitory effect on the gut (transit time, electrolyte absorption, jejunal secretion) has to be hypothesized (24).

Exciting aspects of these therapeutic effects of SMS 201-995 were the shrinkage of the primary tumor or hepatic metastases in a minority of patients (25, 26). It is too early to conclude whether this anti-tumor effect of the analogue will contribute to a prolongation of the survival of these patients.

The future of SMS use would probably become clear after receptor studies (27) giving prevision on the usefulness and the efficacy of this promising hormonal therapy.

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2.

An Aging Mankind in a Fragmented and Integrated New World

PROFESSOR EGON DICZFALUSY
Karolinska Institutet, Stockholm, Sweden.

Magnifice Rector, excellentissime Decanus, Members of the Senate, ladies and gentlemen! To live to see the day, when your old Alma Mater confers on you its highest distinction, an honorary doctor's degree, is a very exceptional privilege given only to a few in this life and the occasion fills me both with gratefulness and with humbleness.

On a solemn occasion like this, the honorary doctor is expected to look back on his scientific career and sum up his contributions. However, to-day is a very special occasion ; the day when Szent-Györgyi Albert received the Nobel Prize exactly half a century ago. And 30 years ago the same Szent-Györgyi Albert said that there is but one safe way to avoid mistakes ; to do nothing, or at least, to avoid doing something new. In his spirit, I intend to do something new and instead of looking back to my professional life, I will look forward to the great tasks confronting the new generation of scientists here and elsewhere.

In his History of the World, in 1614, Sir Walter Raleigh makes the somewhat acid remark that "It is not Truth, but Opinion that can travel the World without a passport", which immediately gives rise to the classical reflection: what is truth? The Danish Nobel Laureate in physics, Niels Bohr perceived very well the complexity of the proposition, when he spoke about two sorts of truth : trivialities, where opposites are obviously absurd, and profound truths, recognized by the fact that the opposite is also a profound truth, and our times provide many examples of this.

Fifty years ago, as a student of Latin at the Klauzál Gábor reálgimnázium in Szeged I came across the well known quotation : Tempora mutantur, et nos mutamur in illis ; times change, and we change with them. Now 50 years later, I feel that we do not change with the same speed as our times. The changes around us are accelerating so rapidly that our perception of these changes is lagging more and more behind. The real danger is that our perception of the consequences of these changes may be affected even more.

It took mankind a long time, perhaps 300,000 years, or more, to reach the first billion ; then growth accelerated and — as you know — we have reached 5 billion this year. All projections of the United Nations (UN) indicate that population growth will continue at a gradually slower rate until it stabilizes at 11 billion sometime around the year 2100. Approximately 90% of this future growth will occur in the developing world.

For the time being, the growth rate is still extremely high in Africa and in the Eastern Mediterranean region, and the population density is by far the highest in South East Asia. (Table 1.)

Year	Billions	
1850	1	
1930	2	
1961	3	
1976	4	
1987	5	
2000	6.15	(4.9)
2025	8.3	(6.9)
2050	9.78	(8.4)
2100	10.87	(9.5)

Table 1. Population growth until the year 1987 and projected populations until 2100. Figures in parentheses stand for developing countries.

During the next 19 years the world population will increase by 1.7 billion; more than half of this increase will take place in 10 countries ; in some of them like Nigeria and Ethiopia, the population will double during this time. The effect of this growth on the already very low economic level remains to be seen. (Table 2.)

COUNTRY	POPULATION IN MILLIONS			GNP US$m
	1986	2006	Increase	
India	775	1036	261	260
China	1074	1320	246	310
Nigeria	99	200	101	730
Indonesia	168	228	60	540
Bangladesh	104	164	60	130
Brazil	138	196	58	1720
Pakistan	104	159	55	380
USSR	281	328	47	n.a.
Ethiopia	38	79	41	110
Mexico	81	121	40	2040

Table 2. Projected population increase between the years 1986 and 2006 and the per capita gross national product in 1984 in 10 selected countries.

What kind of world is then our world to-day? One-third of the households of this world are headed by women and women constitute one-third of the world's labour force. Women are responsible for nearly two-thirds of the total hours worked, receive only 10% of the world's income and own less than 1% of its property. — Another unsolved global problem is unemployment. The International Labour Organization estimates that between 1980 and 2000 employment must be found for 700 million new entrants into the labour force, approximately twice the number of the 1960—1980 period. Moreover, a backlog of unemployed and seriously underemployed workers need jobs. This group constitutes one-third of the existing labour force of 1200 million.

Paradoxically, when expressed in percentage terms, mankind never had such a good life as to-day, but, in absolute numbers, so many never lived in absolute poverty, which traps almost one billion people, 20% of the world population.

Ninety per cent of them live in rural areas ; more than 50% are small farmers and almost 25% are labourers without land.

What can they do? They move to the big cities, and the urban population is increasing dramatically in many developing countries. And since it is the poorest people who move, the population of the slum areas is also dramatically increasing. (Table 3.)

Country	Year	
	1965	1984
Argentina	76	84
Chile	72	83
Colombia	54	57
Hungary	43	55
Libya	29	63
Mexico	55	69
Peru	52	68
Turkey	32	48
Zambia	24	28

Table 3. Increase of urban population as per cent of total in 9 selected countries between 1965 and 1984.

Adequate shelter has been universally recognized as a basic human right; nevertheless, the WHO points out that the overall conditions of shelter and basic services for more than 1 billion of the poor and disadvantaged in developing countries is deteriorating rapidly. Furthermore, some 100 million people have no shelter at all ; they sleep in the streets, under bridges, in vacant lots and doorways.

All UN — projections indicate that urbanization will continue at an increasing rate. In 1974 there were only 28 big cities with a population of 4-million, 15 of them in the developing world. By 2025 there will be 135 such cities and 114 of them will be in developing countries. By 2025, two-thirds of mankind will be city-dwellers.

The UN High Commissioner for Refugees estimates that there are between 10 and 15 million refugees in the world. Their number is increasing at a rate of about 3000 per day ; half of them are children. The top ten countries with the highest number of refugees and their gross national products are shown in (Table 4.) I doubt that comments are necessary.

It may perhaps surprise some of you that the number of physically, mentally, or sensorially disabled persons in the world is between 340 and 480 million : 7—10% of the world population. Some 35% of them live in developing countries. — The state of malnourishment is more difficult to assess, since estimates vary with the definitions and methods of measurement used. However, the WHO thinks that at least 430 million people are affected ; almost 10% of the world population.

At United Nations Conferences some governments are consistently voicing an optimistic view ; they point out that — on the average — fertility has declined, life expectancy increased, caloric intake improved, literacy increased, morbidity diminished and health care improved. Indeed, this is true. However, the opposite is also true.

We are back to the game of percentages and absolute numbers. The percentage of illiterate adults has decreased, but their absolute number increased.

Country	Refugees in thousands	GNP
Pakistan	2,702	380
Iran	2,300	n.a.
Sudan	1,164	360
United States	1,000	15.390
Somalia	700	260
Canada	353	13.280
Zaire	283	140
China	280	310
Burundi	268	220
Tanzania	213	210

Table 4. The top ten countries with the highest number of refugees as of Jan. 1. 1986 and their gross national product (GNP) in 1984. (n.a. — not available).

As you may know this is the UN — decade of safe drinking water and appropriate sanitation and — due to major efforts by the WHO and the World Bank — by the end of the decade, in 1990, there will be an impressive increase in the percentage of adequately covered population.

Due to the above efforts, it is expected that 1.5 billion people will have access to safe drinking water and almost 1 billion to appropriate sanitation. Those still unserved will be 1.2 and 1.8 billion, respectively. These figures do not differ from those reported before the UN — decade. What has happened? The simultaneous population increase has "eaten up" the impressive results. (Table 5.)

Population covered

	Urban				Rural			
	Water		Sanitation		Water		Sanitation	
Year	Mill.	%	Mill.	%	Mill.	%	Mill.	%
1970	307	65	269	34	158	13	140	11
1980	509	72	386	54	472	32	206	14
1985	672	77	518	60	581	36	252	16
1990	835	79	652	62	688	41	298	18

Table 5. Drinking water supply: population covered and access to appropriate sanitation in developing countries (both excluding China). Absolute numbers are given in millions (Mill.) and percentages indicate the ratio of population covered.

When it comes to health care, the population per physician dramatically diminished in the world's most populous countries between 1965 and 1981 ; in parenthesis, the USSR and Hungary have the highest number of physicians in relation to their population. At the same time, however, a significant worsening occurred in several developing countries, as indicated on the right. (Table 6.)

Country	Year	
	1965	1981
China	3780	1730
India	4860	2610
USSR	480	260
United States	640	500
Indonesia	31820	11320
Brazil	2180	1200
Japan	970	740
Bangladesh	n.a.	9010
Nigeria	44990	10540
Pakistan	3160	3320
Hungary	630	320
Ethiopia	70190	88120
Malawi	46900	52960
Mozambique	21130	33340
Uganda	11080	22180

Table 6. Population served by one doctor in selected countries in 1960 and 1981. (n.a. — not available).

There has been a dramatic increase in life expectancy at birth around the world during the past 20 years ; it increased by more than 10 years in many developing countries; and the UN projections indicate that by the year 2025, the global life expectancy at birth will be 70 years, instead of 55, which was the case 13 years ago, in 1974. (Table 7.)

Country	Population (millions)	Year	
		1965	1984
China	1030	59	70
India	749	44	55
USSR	275	74	74
United States	237	74	80
Indonesia	159	45	56
Brazil	133	59	67
Japan	120	73	80
Bangladesh	98	44	51
Nigeria	96	43	51
Pakistan	92	44	50

Table 7. Life expectancy at birth in the most populous countries in 1965 and 1984. Population as in 1984.

As a consequence, dependency ratios will also change. To-day there are 91 children and 6 elderly per 100 adults in Africa and 36 children and 16 elderly in Europe. Furthermore, in aging Europe there are 45 elderly people per 100 children, the highest ratio in the world. The UN projects that by 2025 as much as 23% of the

population of the industrialized countries will consist of people aged 60 or above and that in developing countries their number will double from 6 to 12%.

Already to-day, the life expectancy at birth exceeds 60 years in 98 of the 166 member states of the WHO, which corresponds to 62% of the 5 billion living to-day. As late as in 1950, the global population of the elderly was only 200 million ; 80 million of them lived in developing countries. By 2025 there will be 1.1 billion elderly and almost 800 million of them in developing countries.

There is a similarly accentuated increase in the number of women approaching the menopause ; in 1960, their number was 330 million worldwide ; by the year 2000, their number will exceed 700 million. This will have a profound impact on health service requirements. Among the disorders associated with aging and the menopause, the major ones are osteoporosis, cardiovascular diseases, musculoskeletal disorders, cancer and senile dementia.

The best statistics are from the United States, where osteoporosis affects an estimated 24 million people ; it afflicts half the women over 45 years and 90% of women over 75 years. It is the underlying cause of 1.3 million bone fractures each year. The annual cost of osteoporosis and osteoporotic fractures in the United States in 1985 was between 7 and 10 billion US dollars.

Of the 1.3 million fractures more than 210,000 are hip fractures; those are associated with more deaths, disability and medical costs than all other osteoporotic fractures combined. Men are also afflicted : among those who reach the age of 90, 32% of women and 17% of men will suffer a hip fracture. Most patients fail to recover normal activity, and mortality within 1 year approaches 20%.

For the time being, the only effective method of prevention in women is the administration of estrogen — which is not without other problems — in combination with calcium and exercise. Many other agents are under study, for instance for providing prevention in men. How many women might be affected by osteoporosis in developing countries is unknown ; black and Asian ethnicity appear to reduce the risk. Epidemiological studies in developing countries are urgently needed in order to assess the future needs for health services.

What about cardiovascular diseases? Of the 51 million people who die annually worldwide approximately 25% die of circulatory and degenerative diseases. In the industrialized countries the percentage is more than 50%; in addition, almost 20% die of neoplasms.

Recent reports to the WHO indicate a considerable reduction in death rates from cerebrovascular and ischaemic heart diseases in certain western countries and a disturbing increase in other countries, among others Hungary. The reasons for these opposite trends are incompletely understood (Table 8.)

The same trend can be observed in more than 60 other cardiovascular diseases both in men and women. Because of the overwhelming size of the underlying risk (almost 15 per cent of all women around the world are at risk), in-depth epidemiological studies on the effect of estrogens with or without added progestogens in different populations would be very important. (Table 8.)

Thirty years ago, Szent-Györgyi addressed the issue of the third largest disorder of aging, saying that "Most human suffering, at present, is caused by the so-called 'degenerative diseases' — the name standing for 'diseases we don't understand and, consequently, can do nothing about". He strongly advocated more basic research in this field. Thirty years later the prevalence and pathogenesis of

Country	Period	Cardio-vascular		Cerebro-vascular		Ischaemic heart	
		male	fem.	male	fem.	male	fem.
Japan	1972–82	−36	−42	−51	−51	−22	−34
Australia	1971–81	−32	−39	−39	−44	−33	−36
USA	1970–80	−28	−30	−45	−42	−36	−39
Italy	1970–80	− 9	−28	−20	−28	+ 1	−20
Sweden	1972–82	− 2	−20	−21	−24	+ 5	−19
Yugoslavia	1971–81	+24	+13	+ 7	−2	+35	+13
Poland	1970–80	+31	+ 8	+62	+37	+58	+43
Hungary	1972–82	+33	+ 3	+59	+23	+38	+ 6

Table 8. Percent changes in death rates for 40–69 year male and female (fem.) age group from cardiovascular (ICD 390–485), cerebrovascular (ICD 430–438) and ischaemic heart diseases (ICD 410–414) during 10-year periods in several industrialized countries. ICD-International Classification of Diseases.

rheumatic and degenerative musculoskeletal disorders and the possible usefulness of estrogen therapy are still the big unknowns.

And the cancer issue? Neoplasms are responsible for at least 5% of all deaths in developing countries and almost 20% in industrialized countries. The most frequent cancer types in men are those of the lung, stomach, colon and rectum, whereas in women the ranking order is breast, cervix and stomach. According to the WHO, there has been an alarming increase in lung and breast cancers among women in 28 industrialized countries during the past 20 years. Smoking is a well-established risk factor lung cancer ; concerning risk factors for breast cancer, there still is a great deal of uncertainty (Table 9.).

	Year		Growth
Carcinoma	1960	1980	(%)
Lung	22,000	66,000	200
Breast	44,000	74,000	60
Cervix	23,000	22,000	−5
Stomach	84,000	72,000	−15
Misc.	311,000	442,000	42
Total	514,000	720,000	40

Table 9. Cancer caused mortality of women in 28 industrialized countries.

A few words about senile dementia. Most estimates for the more severe degrees of dementia among those aged 65 and over are between 5 and 8% and the lifetime cumulative risk of becoming severely demented by the age of 80 years has been calculated to be between 15 and 20%. In the United States, more than half the total of over 1 million persons living in geriatric institutions suffer from mental impairment and a high proportion of them require either maximum or intermediate grade nursing care.

Field studies in Western Europe indicate that institutional cases make up less than 10% of the total prevalence of psychiatric disorders in people aged 65 and above and that even in cases of psychoses and severe dementia less than 20% are in institutional care at any give time.

According to demographic projections, the total number of affected persons will increase over the next 50 years by about 50% in the industrialized countries and will more than double in the developing countries. Furthermore, the population over 80 years of age, which suffers the highest frequency of demential disorders, will double in size by the end of this century and the WHO fears that the burden placed by the patients on their families and on the health and social services may be greater than they can bear.

Is then the future hopeless? Absolutely not! However, entirely new approaches and an intelligent collaboration with the inevitable will be required. The UN Conference on Aging expects that, as men and women live to increasingly higher ages, major disabilities will largely be compressed into a narrow range just prior to death. However, to achieve this, it is inevitable to spend much more on health services and on medical research. Only one-third of the 166 member states of the WHO spend to-day more than 5% of their GNP on health : figures of this magnitude will be grossly inadequate to cope with the health problems of a rapidly changing world.

Hence, it will be inevitable to rearrange the national priorities and spend on arms and armaments much less and on health services much more. There is simply no viable long-term alternative, and developing countries will soon realize this. (Table 10.)

Expenses spent on	Developed Countries		Developing Countries	
	1970	1978	1970	1978
Arms and Armament	312	345	70	102
Health and Medical Services	126	213	13	22

Source: UNEP, 1984

Table 10. Expenses spent on armament and health services (USD M).

For the same reason, it became easy to answer the question posed by Adlai Stevenson at the UN General Assembly 25 years ago : 'Will Man ever recognize that his need for his fellow men far outweigh his arguments with them?" Yes, he will. There is simply no long-term alternative. And we have to keep in mind, that our lifetime represents the first age since the dawn of civilisation in which people have dared to think it practicable to make the benefits of civilisation available to the entire human race, and what happens to-day in terms of industrialized country assistance to developing countries is just the very beginning of a process, which is — again — inevitable.

Am I a naive optimist? A dreamer? Certainly not. I am only consistent. Looking back on history, Lesher and Howick say that 'Eight hundred life spans can bridge more than, 50,000 years. But of these 800 people, 650 spent their lives in caves or worse ; only the last 70 had any truly effective means of communicating with one another, only the last 6 ever saw a printed word, or had any real means of

measuring heat or cold. Only the last 4 could measure time with any precision ; only the last 2 used an electric motor ; and the wast majority of the items that make up our material world were developed within the life-span of the eighthundredth person, our own generation.' All of us could add something significant to this list, be it the airplane, radio, television, the conquest of space, chemotherapy of various cancers, bacterial and viral diseases and the eradication of many infectious diseases. Most drugs we use to-day have been developed within our lifetime. Thus science has radically changed our world; it will change even more the world of next generations and will improve the human condition on Earth. The process is inevitable; hence there is plenty of hope for the future.

Ladies and gentlemen, in the final analysis, hope is the quintessence of the human condition, and I believe that each of us has many opportunities in this life to generate new hope. I also believe that the collection, systematisation and dissemination of scientific information and the generation of fresh hope are crucial steps toward improving the human condition to-day and to-morrow. This will also be the task confronting you, the new generation of scientists. And in your future endeavour, please do not forget that medical research is also an essential ingredient of our culture. Therefore remember the words of Kodály Zoltán: Culture cannot be inherited. The culture of one's forefathers evaporates in a trice if each generation does not acquire it over and over again for itself." — I am convinced, that the Albert Szent-Györgyi Medical Unviersity will successfully maintain the cultural treasures of Hungary and further develop them in the centuries to come.

3.

Bedeutung physikalisch-chemischer Parameter für die Arzneiformulierung von

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Magnifizienzen, Spectabilitäten, meine sehr verehrten Damen, meine Herren, liebe Kolleginnen und Kollegen!

Ich erlaube mir, die Entwicklung der Pharmazeutischen Technologie — vor allem für die Jüngeren im Auditorium für die vergangenen 30 Jahre — anhand meiner Person deutlich zu machen.

Meine Generation besaß am Ende des 2. Weltkrieges im Fachgebiet Gelenik keine Hochschulausbildung. Die Kenntnisse der Galenik (so hieß die Pharmazeutische Technologie damals in Deutschland) resultierten aus dem damaligen obligatorischen zweijährigen Vorpraktikum.

Hier erlernte ich das defekturmäßige Herstellen von apothekenüblichen Arzneiformen. Der Vorpraktikant hörte, je nach der Qualität des die Ausbildung betreuenden Apothekers, vielleicht auch einmal etwas über physikalisch-chemische Prozesse bei der Arzneiformung.

Während der Hochschulausbildung gab es keine theoretische Vorlesung in diesem Fach. Einige kleine praktischen Übungen zu Inkompatibilitätsfragen waren alles, womit man auf diesem Gebiet der Galenik während des Studiums konfrontiert wurde.

Deshalb betrieb man das Gebiet empirisch.

Die Ausbildung erfuhr ab Mitte der 50-iger Jahre in der DDR eine grundlegende Veränderung.

Dieses Gebiet war seit dieser Zeit in Theorie und Praxis voll in den Ausbildungsgang der Pharmazeuten integriert, wobei zunächst immer noch die Herstellung der Arzneiformen im Apothekenmaßstab im Vordergrund stand.

Als Student war ich in den Vorlesungen von Prof. Dr. Dr. h. c. mult. Kurt Mothes fasziniert, der mich in den Fächern Pharmakognosie und Biochemie der Pflanzen durch seinen überzeugenden Vortragsstiel begeisterte. So war es nicht verwunderlich, daß sich meine ersten wissenschaftlichen Arbeiten mit der Biosynthese der Kumarine in Solanaceen befaßten und von Kurt Mothes im Rahmen einer Dissertation betreut wurden.

Nach erfolgter Promotion erhielt ich einen Lehrauftrag für das Gebiet der organischen Arzneimittelanalyse.

Da ich immer der Auffassung war und auch heute noch bin, daß Lehre und Forschung eine Einheit zu bilden haben, änderte ich mein Forschungsgebiet.

Entsprechend meines Einsatzes in der Lehre bei der Ausbildung von Pharma-

ziestudenten, arbeitete ich nun an analytischen Fragestellungen zur Standardisierung von Arzneistoffen und Arzneiformen.

Diese Arbeiten haben z.T. Eingang in den allgemeinen Teil als auch in Monografien für das Arzneibuch der DDR gefunden.

Ich habilitierte mich mit einer Arbeit zu Standardisierungsfragen von quecksilberfreien Diuretica und von Sulfonamiden.

Ich war mit analytischen Methoden auf dem Gebiet der Arzneistoffe und der Arzneiformen bestens vertraut.

Durch meine Forschungsarbeiten habe ich damals z.B. die IR-und UV-Spektroskopie und die wasserfreie Titration für bestimmte Arzneistoffe und -formen nutzbar gemacht.

Bei der praktischen Ausbildung der Studenten hatte ich mich aber auch über Jahre in der Betreuung des galenischen Praktikums für das 5. und 6. Studienjahr betätigt.

So kam ich schließlich als gelernter Analytiker über die Forschungsarbeiten auf dem Gebiet der Arzneiformen-Standardisierung 1965 endgültig zur Pharmazeutischen Technologie.

In dieser Zeit verlagerte sich in immer stärkerem Maße die Herstellung der Arzneiformen in den halbindustriellen und in den industriellen Bereich.

Damit mußte sich das Fach endgültig von der oft auf Empirie beruhenden Herstellung der Arzneiformen im Apothekenmaßstab lösen.

Die Palette der Arzneizubereitungen wurde dabei gleichzeitig durch eine Reihe von modernen Arzneiformen bereichert und auch für die Zukunft sind nutzbringende, effektive Lösungen hier für dieses Gebiet zu erwarten.

Neue Wirkstoffträger und Hilfsstoffe, neue Arbeitsverfahren und der damit verbundene ständige Fortschritt auf dem Sektor der Apparate-, Maschinen- und Automatentechnik sowie die kontinuierliche Verbesserung der Methoden und Geräte zur Prüfung der Arzneiformen gaben diesem pharmazeutischen Fachgebiet ein neues Profil.

Damit kam die Erkenntnis zum Tragen, daß ein Arzneistoff erst dann ein optimal wirkendes Arzneimittel werden kann, wenn er in geeigneter Weise zu einer Arzneiform verarbeitet wird. Gleichzeitig erschließen sich dadurch neue Möglichkeiten für bereits bekannte Arzneistoffe.

Dieser Prozeß beruht nicht zuletzt auf der umfassenden Einbeziehung mathematisch-physikalisch-chemischer Grundlagen über Arzneistoffe, Hilfsstoffe und industrielle Verfahren und deren mögliche Wechselbeziehungen und auf der Entwicklung der Biopharmazie. Alle die damit zusammenhängenden Fragen bezeichnen wir heute als den Komplex der Arzneiformulierung.

Aus diesen Gründen waren wir der Auffassung, daß der alte Name "Galenik" für dieses ehemals empirische Arbeitsgebiet nicht mehr zutreffend sei und führten dafür als Bezeichnung "Pharmazeutische Tehnologie" in der DDR ein.

Die Älteren von Ihnen werden sich erinnern, daß ich vor etwa 20 Jahren hier in Szeged einen Vortrag zu Fragen der Aufgaben der pharmazeutischen Technologie gehalten habe. Ich brachte damals meine Auffassung zum Ausdruck, daß abgesehen von der rein technischen und verfahrenstechnischen Seite das Arbeitsgebiet Pharmazeutische Technologie eine pharmazeutisch angewandte Physikalische Chemie zu sein habe.

Von dieser Auffassung bin ich nie abgewichen.

So bearbeitete ich von 1967 zusammen mit meinen Mitarbeitern des von mir geleiteten Wissenschaftsbereiches Pharmazeutische Technologie der Sektion Phar-

mazie der Martin-Luther-Universität Halle im Rahmen von Vertragsforschungsarbeiten mit der Pharmazeutischen Industrie der DDR Fragen der Arzneiformulierung für feste Peroralia und löste damit die vorher vorhandenen 18 Forschungsverträge dieses Bereiches auf den unterschiedlichsten Gebieten der Arzneimittelforschung ab.

Konzentriert für die festen Peroralia wurden unter meiner Leitung seitdem Optimierungsfragen, neue Herstellungsverfahren, der Einsatz von neuen Hilfsstoffen auch hinsichtlich der Erzielung von protrahiert wirkenden Arzneiformen, Auflösungs- und Liberationsprobleme der Arzneistoffe aus der Arzneiform und andere physikalische und physikalisch-chemische Parameter als pharmazeutisch-technologisch interessante Parameter bearbeitet.

Für biopharmazeutisch relevante Aspekte bearbeiteten wir zahlreiche Freigabemodelle für in vitro-Untersuchungen.

Zur gleichen Zeit, also von 1967 an, gedieh eine fruchtbringende Kooperationsarbeit mit einer Arbeitsgruppe um KEDVESSY und SELMECZI des Pharmazeutisch-Tehnologischen Institutes der Medizinischen Universität Szeged, die sich in ihrer Intensität immer mehr verbesserte und die im letzten Jahrzehnt eine vertragliche Basis hatte.

Es sei mir an dieser Stelle erlaubt festzustellen, daß diese kollegiale Zusammenarbeit dazu beigetragen hat, zwischen dem Pharmazeutisch-Technologischen Institut der Medizinischen Universität Szeged und dem Wissenschaftsbereich Pharmazeutische Technologie der Sektion Pharmazie der Martin-Luther-Universität Halle-Wittenberg einen echten wissenschaftlichen Erfahrungsaustausch in Theorie und Praxis zu bewirken und was nach meiner Meinung wichtig ist: Es sind echte, nicht mehr trennbare persönliche Feundschaften zwischen den Kooperationspartnern entstanden, die weit über ein kollegiales Verhalten hinausgehen.

In der jüngsten Vergangenheit ist die Wirkungsintensität und — Dauer eines Arzneistoffes im wesentlichen Maße durch die Arzneiformen beeinflußbar geworden.

Immer stärker wird sowohl bei der Grundlagenforschung als auch bei der angewandten Forschung die Zusammenarbeit der Pharmazeuten mit anderen Naturwissenchaftlern, mit Medizinern und Technikern, insbesondere auch aus den Bereichen der pharmazeutischen Industrie, zunehmen.

Aus der Sicht des Pharmazeutischen Technologen sind bei der Entwicklung einer Arzneiform im Hinblick auf die biologische Verfügbarkeit, auf die Verträglichkeit, auf die Stabilität, auf die kontrollierte Wirkstoffreigabe und auf die Reproduzierbarkeit, sechs Parameter für den jeweiligen Wirkstoff zu optimieren:

1. Applikationsart
2. chemische Form des Wirkstoffes
3. physikalischer Zustand des Wirkstoffes
4. Applikationsform
5. Grund- und Hilfsstoffe
6. Herstellungstechnologie

Bei der Entwicklung von festen peroralen Arzneiformen lassen sich nun prinzipiell 3 Phasen unterscheiden:

1. Präformulierung
2. Formulierung
3. Scaling up

Die optimale Entwicklung von peroralen Arzneiformen (Tabletten, Dragees, Kapseln) mit hoher Bioverfügbarkeit und kontrollierter Wirkstoffreigabe erfordert im Rahmen der Präformulierungsphase die Erarbeitung von physikalisch-chemischen Daten für die Wirksubstanz allein, evtl. auch in Kombination mit zu verwendenden Hilfsstoffen.

Zu diesen sogenannten Grundinformationen gehören Stabilitätsdaten, die chemische Arzneistoff-Hilfsstoff-Kompatibilität und die physikalisch-chemischen Eigenschaften des Wirkstoffes, wie da sind:

— Löslichkeit, initiale Auflösungsgeschwindigkeit, Auflösung von Wirkstoffpulvern (pH-Profil)
— Partikelgröße, -form, -oberfläche
— Polymorphie
— Benetzbarkeit
— Verarbeitungseigenschaften des Wirkstoffes (z.B. Verpreßbarkeit, Fließverhalten)
— pK_a-Wert
— Verteilungskoeffizient
— Permeationsverhalten

Bei schwerlöslichen Arzneistoffen sind besondere Untersuchungen hinsichtlich der Beeinflussung der Lösungseigenschaften durchzuführen und evtl. Möglichkeiten zur Verbesserung der Auflösungsgeschwindigkeit bzw. der Löslichkeit vorzuschlagen, und zwar besonders in den Fällen, wo die Auflösung des Arzneistoffes den geschwindigkeitsbestimmenden Schritt im Prozeß der Liberation/Absorption bei festen Arzneiformen darstellt. In der Regel gilt dabei, daß bei Arzneistoffen mit einer Löslichkeit kleiner als 0,3% die Auflösungsgeschwindigkeit zum geschwindigkeitsbestimmenden Parameter für die Resorption und damit auch als Folge davon für die pharmakologische Wirkung wird.

Am Beispiel entsprechender pharmazeutischer Problemsubstanzen, bei deren pharmazeutisch-technologischer Formulierung Schwierigkeiten bezüglich ihrer pharmakologischen Gleichwertigkeit auftreten können und für die die FOOD and DRUG Administration (FDA) eine 193 Wirkstoffe enthaltende Liste veröffentlicht hat, untersuchten wir in Kooperation mit dem Pharmazeutisch-Technologischen Institut der Medizinischen Universität Szeged in den letzten Jahren die Möglichkeiten der Beeinflussung des physikalischen Zustandes ausgewählter Wirkstoffe, sowie deren Bedeutung für die Herstellung und die Wirkstofffreigabe aus festen Peroralia.

Diese Problemarzneistoffe sind durch folgende Eigenschaften gekennzeichnet:

1. schlechte Wasserlöslichkeit
2. niedrige Dosierung
3. geringe therapeutische Breite
4. verminderte Freisetzung aus Komprimaten

Als Bedingung für die wissenschaftliche Bearbeitung der dargestellten Problematik waren aussagekräftige physikalisch-chemische Festkörperuntersuchungen notwendig, die in unserem Falle durch nationale und internationale Kooperation (Szeged) machbar waren, und für beide Partner eine Erweiterung der Arbeitsmöglichkeiten darstellten. Solche Untersuchungsmöglichkeiten waren im besonderen:

— Röntgendiffraktometrie
— thermoanalytische Verfahren
— Rasterelektronenmikroskopie

— IR- und UV-Spektroskopie
— in-vitro-Modelle
— Für die Verarbeitungseigenschaften nach dem z.B. Direkttablettierungsverfahren sind dann noch weiterhin geeignete instrumentierte Tablettenmaschinen für die Untersuchungen zur Physik der Tablettierung notwendig.

Die im Handel befindlichen Wirkstoff- und Hilfsstoffqualitäten aus unseren beiden Ländern dienten als Grundlage für die differenzierte Herstellung verschieden definierter Kristallmodifikationen von Wirkstoffen als auch röntgenamorpher Formen sowie von Feststoffdispersionen nach modernen technologischen Verfahren z.B. der Sprühtrocknung.

Diese Produkte wurden anschließend hinsichtlich ihrer physikalisch-chemischen und tehcnologischen Eigenschaften untersucht und dem Tablettierprozeß unterworfen.

Da bekanntermaßen durch den Preßdruck und die gleichzeitige thermische Belastung Veränderungen des physikalischen Zustandes der verarbeiteten Produkte möglich erscheinen, war es wichtig, Modelluntersuchungen für diese Festkörperumwandlungen zu erarbeiten.

In der Formulierungsphase der Wirkstoffe zu Tabletten nach modernen Direktkompressionsverfahren charakterisieren wir schließlich die Anwendungsmöglichkeiten von Hilfsstoffen auf der Basis von mikrokristallinen Cellulosen. Diese wurden vor einigen Jahren als indifferente Füllmittel, Bindemittel und Sprengmittel von uns in Tablettenrezepturen eingeführt, besitzen aber -wie die durchgeführten experimentellen Arbeiten zeigen- unterschiedliche plastisch-elastische Eigenschaften und beeinflussen sowohl den Tablettierprozeß als auch die Tabletteneigenschaften und die Wirkstoffreigabe in starkem aber unterschiedlichem Maße.

Die Rezepturoptimierungen für verschiedene Problemarzneistoffe ergaben sowohl verallgemeinerungsfähige Aussagen zum "Know how" der Tablettenentwicklung, als auch die Notwendigkeit spezieller Untersuchungen in Abhängigkeit von physikalisch-chemischen Eigenschaften der verwendeten Wirk- und Hilfsstoffe.

Bei unserer Zusammenarbeit haben wir eine größere Zahl solcher Wirkstoffe mit polymorphen Eigenschaften pharmazeutisch-technologisch formuliert und mittels der genannten Methoden untersucht. Solche Unterfangen sind sehr aufwendig und lassen sich hier nur punktartig skizzieren.

Ich möchte das kurz einmal am Beispiel der Polymorphie des Antiepileptikums Carbamazepin demonstrieren.

Dazu ist z.B. die Herstellung unterschiedlicher polymorpher Formen und des Dihydrats notwendig, was durch Kristallisation, Temperung und Sublimation (siehe Schema 1) erfolgte.

Schema 1

Herstellungsmethoden für die Carbamazepin-Modifikationen I, II, III, IV, und für das Carbamazepin-Dihydrat

Die Charakterisierung der gewonnenen polymorphen Formen und des Dihydrates führten wir mit den im Schema 2 enthaltenden Methoden durch.

Kristallmodifikationen I, II, III, IV
Suspensionen in Lösungsmitteln

g/dl		
1,0 g/dl	Toluen	jeweils in siedenden Wasserbad
2,0 g/dl	Ethylacetat	lösen, bei −18 °C innerhalb von
3,0 g/dl	Aceton	30—40 min rekristallisieren.
5,0 g/dl	Ethanol (96% V:V)	Kristalle bei 60—65 °C vortrocknen
5,0 g/dl	Methanol.	Lösungsmittel
jeweils 100 ml		durch
		Vakuumtrocknung entfernen

Temperierung
Das Handelsprodukt des Carbamazepins wird in dünner Schicht auf Glasplatten 9 h im Trockenschrank bei 140 °C erhitzt.
Sublimation
Das Handelsprodukt des Carbamazepins wird z.B. auf dem Heizblock des Boetius-Heiztischmikroskopes (Typ PHMK 78/1873, VEB Analytik, DDR-Dresden) einer Mikrosublimation 4 h bei einer Temperatur von 180 °C unterworfen.
Dihydrat-Darstellung
Carbamazepin-Kristalle werden in Petrischalen in flacher Schicht bei 100%-iger relativer Luftfeuchte in einem Hygrostaten bei 20 °C — aufbewahrt.

Schema 2
Methoden zur Charakterisierung der nach Schema 2 hergestellten Produkte

Die Beschreibungen der nach dem Schema 1 gewonnenen Modifikationen und des Dihydrates sind im Schema 3 enthalten

Thermoanalyse
— Meßsystem: Differential-Scanning-Calorimeter vom Typ DSC 2 Perkin-Elmer Corp. USA-Norwolk
— DTA-Apparatur: Netzsch-Modell 404 B (Netzsch-Gerätebau GmBH, D-Selb)
— Heiztisch-mikroskopie-Appartur: Boetius-Heiztischmikroskop (Typ PHMK 75/1873, VEb Analytik, DDR-Dresden)

IR-Spektroskopie
— Meßsystem: Beckman IR 12 Infrared Spectrophotometer (Beckman Instruments, USA-Fullterton, CA) Specord 78 IR (VEB Carl-Zeiss-Jena, DDR-Jena)
— KBr-Technik: 2—3 mg Carbamazepin / 250—300 mg KBr werden mit einer Preßkraft von 100 kN zu einer Tablette verpreßt
— Nujol-Technik: 10 mg Carbamazepin werden in 2 Tropfen Nujol suspendiert. Messung mit Hilfe von NaCL-Prismen

Röntgendiffraktometrie
— Philips — Vertikalgoniometer PW 1050/25 (Philips, NL-Eindhoven)
— Hochspannungsgenerator Müller Mikro 1011 Cu Kα-Strahlung, Ni-Filter, 40 KV, 30 mA, Zählrohrbewegung 1° min^{-1} ($=2\Theta$)
— Horizontalgoniometer HZG 4 (Kombinat Carl Zeiss VEB Präzisionsmechanik, DDR-Freiberg)

— Hochspannungsgenerator TUR M 62 (VEB Transformatoren- und Röntgenwerk, DDR-Dresden)
Cu Kα-Strahlung, Ni-Filter, 34 KV, 32 mA, Zählrohrbewegung 0,5° min^{-1} ($=2\Theta$)

Lösungskalorimetrie
Meßsystem: Isoperiboles Kalorimeter LKB 8700-1
Precisions Calorymetry System for Reaction and Solution Calorymetry
(LKB Produkter AB, S-Stokholm-Bromma 1)

Dichtebestimmung
0,4000 g Carbamazepin-Modifikation werden in die Matrize einer hydraulischen Presse gefüllt, der Oberstempel ∅13 mm eingesetzt, die Substanzsäule 60 s evakuiert, dann ein Preßdruck von 737 MPa angelegt und 3 min der Druck gehalten.
Wägung nach Entnahme der Tablette ohne Beschädigung.
Berechnung des Volumens, man erhält die Dichte nach

$$p = m/v$$

p = Dichte ($kg \times m^{-3}$)
m = Masse des Preßlings in kg
V = Volumen des Preßlings in m^3

Die Überprüfung des Verfahrens erfolgte gegen bekannte Dichten (NaCl, Phenobarbital, Sulfathiazol)

Rasterelektronenmikroskopie
nach Kohle- und Goldbedampfung werden am JSM / 35C Scanning Electron Microscope (Jeol — Co.Ltd, J-Tokyo) / REM-Aufnahmen angefertigt.

Schema 3
Beschreibung der nach Schema 1 hergestellten Produkte

Modifikation I
Gewinnung druch:
Umkristallisation aus Ethanol (96% V:V)
Temperung 9h bei 140°C
Sublimation 4 h bei 180°C auf dem Boetius-Heizblock
Schmelzpunkt: 190,5°C
Schmelzenthalpie $\Delta H_F = 24{,}2\ KJ \times mol^{-1}$
Modifikation II
Gewinnung durch:
Umkristallisation aus Toluen
Schmelzpunkt 188,4°C
Schmelzenthalpie $\Delta H_F = 19{,}0\ KJ \times mol^{-1}$
Entsprechend der Schmelzwärmeregel nach BURGER (1) verhalten sich die Modifikationen monotrop.
Modifikation III
Gewinnung durch:
Handelsprodukt

Umkristallisation aus Aceton
Die DSC-Kurve weist im Bereich 162 bis 172°C das Signal einer endotherm verlaufenden Phasenumwandlung der Modifikation III (Raumtemperaturform) in Form I (Hochtemperaturform) auf, die jedoch von Schmelzerscheinungen nicht umgewandelter Form III bei 1976°C begleitet war. (siehe Abb. 1)
Die Umwandlung ist von der Heizrate abhängig.
Bei einer Aufheizung $\leqq 5\ K \times min^{-1}$ erfolgt eine vollständige
Umwandlung von III in I.
Umwandlungsenthalpie $\Delta H_{\ddot{U}} = +2{,}6\ KJ \times mol^{-1}$
Die Form I und III zeigen enantiotropes Verhalten (Umwandlungswärmeregel).
Modifikation IV
Gewinnung durch:
Umkristallisation aus Ethylacetat
Die DSC-Kurve dieser Modifikation zeigt im Temperaturbereich von ca. 130 bis 148°C eine exotherme Phasenumwandlung in die Modifikation I an (siehe Abb. 1).
Umwandlungsenthalpie $\Delta H_{\ddot{U}} = 1{,}6\ KJ \times mol^{-1}$
Das Auftreten des exothermen Umwandlungspeaks zeigt Monotropie zwischen Modifikationen IV und I.
Dihydrat des Carbamazepins
Beim Aufheizen in der Thermoanalyse registriert man im Temperaturintervall von ca. 50 bis 80°C einen breiten Desolvatationspeak (Abb. 1, Kurve D).
Gravimetrisch läßt sich ein Gewichtsverlust von 13% bestimmen, das beweist das Vorliegen des Dihydrates.
Für die Kristallmodifikationen und für das Dihydrat stimmen die Ergebnisse des DSC und der DTA überein

Die Abb. 1 enthält die DSC-Kurven der polymorphen Formen und des Dihydrates des Carbamazepins.

Wir haben natürlich zur Charakterisierung der Modifikationen auch die anderen von mir hier genannten physikalisch-chemischen Methoden benutzt. Im Rahmen des Vortrages sind sie aus Zeitgründen nicht zu demonstrieren, für Interessenten sei die entsprechende Literatur (2, 3) genannt.

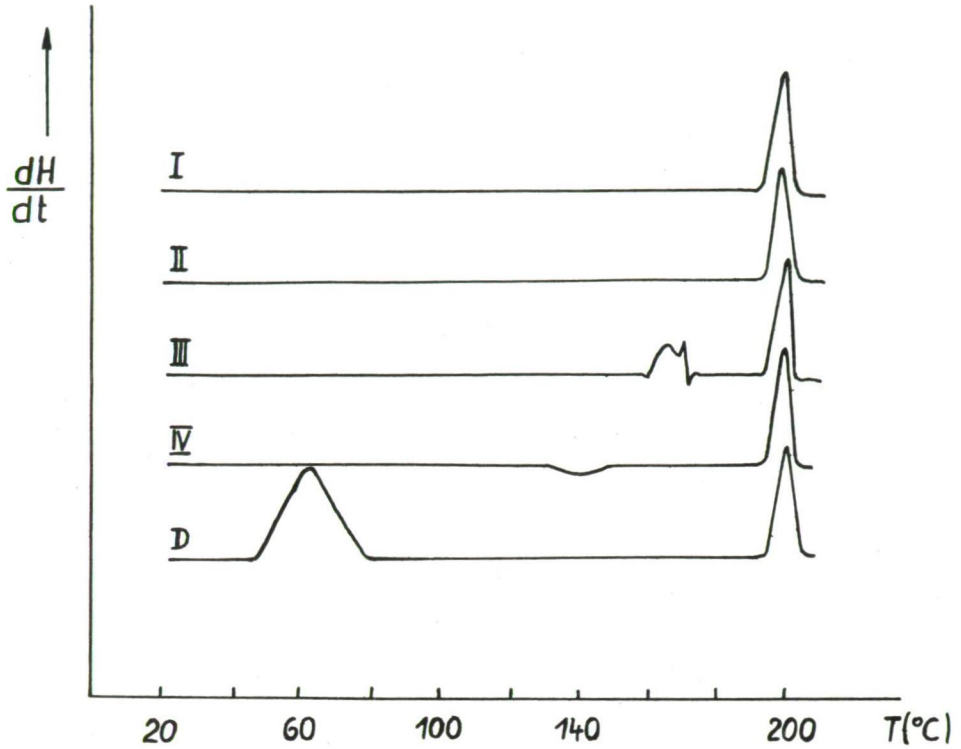
Um den Einfluß verschiedener bei pharmazeutisch-technologischen Arbeiten wirkender Kräfte auf bestimmte Kristallgitter zu untersuchen, unterwarfen wir z.B. die Carbamazepin Modifikationen I, II, III unterschiedlichen Preßkräften bei der Direkttablettierung.

Das kristallografische Verhalten untersuchten wir für die resultierenden Preßlinge mit Hilfe der Röntgendiffraktometrie, der IR-Spektroskopie und der Differential-Scanning-Kalorimetrie. (2)

Die Kristallgitter der untersuchten Modifikationen weisen gegenüber den Preßkräften eine unterschiedliche Stabilität auf, was in der Analogie zur Krafteinwirkung durch Mahlungsversuche des Carbamazepins steht.

Die Modifikation II ist gegenüber mechanischer Belastung (Mahlung, Tablettierung) instabil, die Modifikation I wandelt sich nur unter forcierten Arbeitsbedingungen um. In beiden Fällen entsteht aber die mit 1340 kg/m^3 die größte Dichte besitzende Modifikation III.

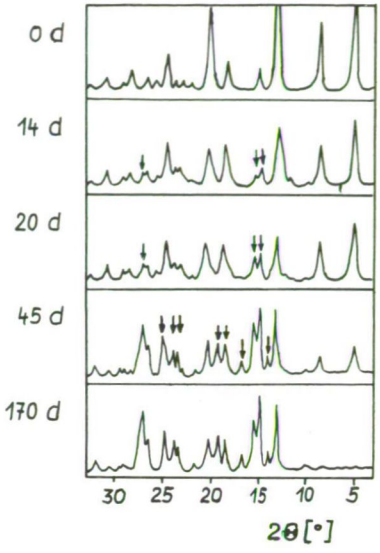
Abbildung 1
DSC-Kurven der Carbamazepin-Modifikationen und des Dihydrates Heizrate 10 K min^{-1}



Dagegen wird bei den von uns gewählten Versuchsbedingungen (Kompression 20, 50, 100 kN) das Kristallgitter der Modifikation III nicht soweit verändert, daß sie in eine andere Modifikation übergeht. (3)

Bei der Preßkrafteinwirkung unter genormten Bedingungen auf die Kristalle der Modifikation II trat eine preßkraftinduzierte Modifikationsumwandlung auf, die die schon früher von uns getroffene Feststellung, daß unter dem Einfluß der Preßkraft eine Modifikationsumwandlung polymorpher Arzneistoffe nur initiiert wird, erneut unterstreicht (s.Abb.2). (4)

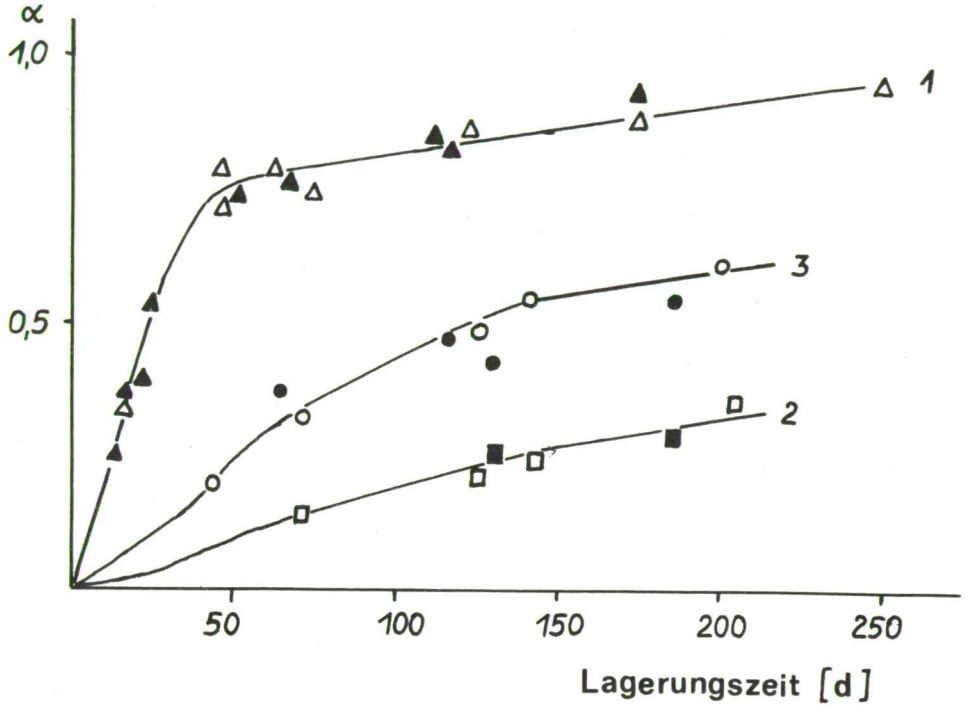
Abbildung 2
Röntgenbeugungsdiagramme für die mit 100 kN verpreßte Carbamazepin-Modifikation II in Abhängigkeit von der
Lagerungsdauer
Pulveraufnahmen



Die Umwandlung ist dabei von der Größe der angewandten Preßkraft abhängig, wobei nach unserer Auffassung in Relation zur Preßkraft eine Defektsituation im Kristallgitter der Ausgangsmodifikation auftritt.

Mit der Erhöhung des Preßdruckes nehmen die Gitterstörungen zu, so daß die mit 100 kN verpreßten Proben über eine größere Anzahl von Keimbildungsstellen im Vergleich mit den 20 und 50 kN verpreßten Proben verfügen, woraus dann die von uns beobachteten Umwandlungsgeschwindigkeiten in die bei Raumtemperatur stabile Modifikation III resultieren (s.Abb.3).

Abbildung 3
Preßdruckinduzierte Phasenumwandlung für die mit 20 kN (2), 50 kN (3) und 100 kN (1) komprimierte Carbamazepin-Modifikation II in die Form III in Abhängigkeit von der
Lagerungsdauer bei Raumtemperatur, durch DSC (offene Symbole) und mittels Röntgendiffraktometrie (gefüllte Symbole) ermittelt.
α = Umwandlungsgrad



Aus den genannten Gründen sind nach unserer Auffassung Aussagen über das Ausmaß von Modifikationsumwandlungen nur dann sinnvoll, wenn gleichzeitig der Untersuchungszeitpunkt eine Berücksichtigung findet.

Aus der phänomenologischen Darstellung einer Phasenumwandlung, z.B. durch die Darstellung von zu unterschiedlichen Zeiten aufgenommener Röntgendiffraktogramme, kann der Umwandlungsgrad bestenfalls abgeschätzt werden. Aussagen zum zeitlichen Verlauf der Kinetik sind nur durch eine kontinuierliche Messung der Umwandlungsrate mit Hilfe geeigneter Methoden möglich.

Sind nun die hier von mir angerissenen Probleme durch die Gundlagenforschung gelöst und nach Rezepturoptimierung, die man heute mittels mathematischer Methoden (z.B. mit dem 2^3 Design) durchführt, wird die Arzneiform hergestellt und die in vitro-Liberation des Wirkstoffes aus der Arzneiform festgestellt.

Mit der Prüfung der Lösungsgeschwindigkeit ist dann die Entwicklungsarbeit abgeschlossen, die Prüfung sollte in Zukunft bei allen festen Arzneiformen in der

Formulierungsphase als Routineprüfung nach einer offizinellen Methode durchgeführt werden. Sie schließt sowohl die klinischen Versuchspräparate als auch die künftige Handelsform ein und stellt in immer stärkerem Maße die Grundlage für eine künftige in vitro/in vivo Korrelation dar.

Die Kenntnisse von Zusammenhängen zwischen in vitro-Daten und entsprechenden in vivo-Befunden wird in Zukunft ein immer wesentlicheres Hilfsmittel für den Pharmazeutischen Technologen hinsichtlich der Rezepturoptimierung werden, da jede Entwicklungsarbeit immer stärker von einer bestimmten Zielrichtung der Arzneistoffliberation ausgeht.

So kann es sinnvoll sein, einen Wirkstoff möglichst schnell in Lösung zu bringen, wie es für die große Zahl der Problemarzneistoffe gilt, um die Bioverfügbarkeit zu verbessern.

Umgekehrt ist für Substanzen mit mehr oder weniger schneller Elimination anzustreben, die Freisetzung zu verzögern, um dadurch länger anhaltende Blutspiegel zu erzielen oder die Nebenwirkung von Wirkstoffen zurückzudrängen.

In der Phase der Scaling up erfolgt schließlich die Überführung des Herstellungsverfahrens einer Arzneiform vom Labormaßstab in den Produktionsmaßstab.

Auf der Grundlage der gesammelten Erfahrungen während der durchlaufenden Präformulierung- und Formulierungsphase sollten die wichtigsten Eigenschaften des Endproduktes nicht oder nur wenig verändert werden, um die biologische Verfügbarkeit und damit die therapeutische Wirksamkeit des Präparates zu sichern.

Daher ergeben sich insbesondere bei nicht homogenen Arzneiformen, dazu gehören auch die Tabletten, besondere Probleme bei der endgültigen Aufstellung der Fabrikationsvorschrift.

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4.

How Do Neurons Choose Partners for Communication?

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In complicated interactive systems, and this includes the nervous system, choosing partners is one of the most difficult tasks. Since I do not speak your beautiful language I shall continue my lecture in the language which has most often served in partner-links between researchers over the last few decades.

Bonyolult interaktív rendszerekben, így az idegrendszerben is, a partnerválasztás a legnehezebb feladatok közé tartozik. Mivel nem beszélem az Önök szép nyelvét, előadásomat azon a nyelven folytatom, mely az utóbbi évtizedekben a kutatók közötti partnerkapcsolatokat leginkább szolgálta. — Let me therefore switch to English.

In complex interactive systems, even more than selecting a suitable language, it is difficult to choose appropriate partners for communication. The following example may elucidate the type of difficulty which arises: A fruitful partnership has been established between the Albert Szent-Györgyi University and the University of Göttingen. We would probably run into serious problems, if we were asked to explain the success of this partnership merely by evaluating the overall structures and functions of the two institutions involved. On the other hand, it is obvious that much of this success is based on cooperation between individual scientists and laboratories. Thus, the functional significance of local interactions apparently increases, when they fit the needs of both the whole system and the interacting components.

Similarly, neurobiological research has provided much evidence indicating that brain functions are closely related to interactions between specific sets of nerve cells. The functional development of the brain should then critically depend on how nerve cells choose partners for communication. This question includes three suppositions: nerve cells are capable of communication; nerve cells have specific communication partners; and nerve cells participate in the choice of their partners. I shall briefly discuss the validity of these assumptions, before we shall try to find an answer to the key question: Which criteria do nerve cells use for selecting communication partners?

The first assumption, *nerve cells are capable of communication,* is based on characteristic properties of nerve cells or neurons. These may be summarized as follows:

— Nerve cells release and receive signals

— Signal transfer between neurons by "chemical transmitters" is directed through cell-to-cell contacts ("synapses") (Fig. 1).

— Nerve cells are polarized between transmitting and receiving modules which spatially separate the "pre- and post-synaptic elements" of each neuron.

— Two types of post-synaptic effect ("excitation" and "inhibition") are mediated by separate neuron populations.

— Synaptic messages regulate the probability of signal formation by disturbing the excitation-inhibition balance in the receiving neuron.

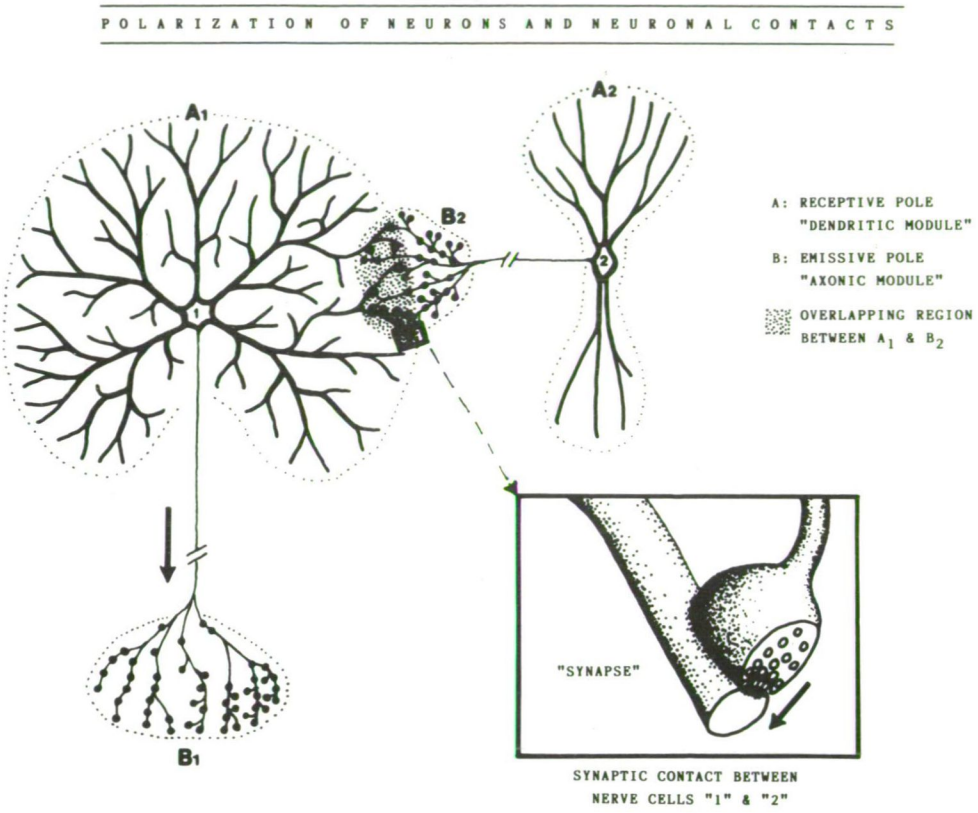

Fig. 1: Neurons are polarized cells. Presynaptic and postsynaptic elements spatially separate and accumulate (axons and dendrites, respectively). "Synapses" are contacts between pre- and postsynaptic elements which are specialized for directed signal transfer by chemical transmitters. Synaptic connections between neurons are restricted to the overlapping region between their "receptive" and "emissive" poles.

Thus, nerve cells indeed show cytological characteristics which make them suitable for intercellular communication. Apparently they form a cable-communication system with plug-and-socket-like contacts through which they may exert excitatory or inhibitory effects on each other.

The second question is, whether or not *nerve cells have specific communication partners*. There is an enormous complexity of intercellular connections in the nervous system and many of these connections may be neither stable nor specific. However, physiological, chemical and anatomical data suggest that neurons may have highly specific connections which characterize their function. We then have to ask: How specific are connections between neurons?

— Between all neurons, connections are restricted by the range of their cell processes (Fig. 2).

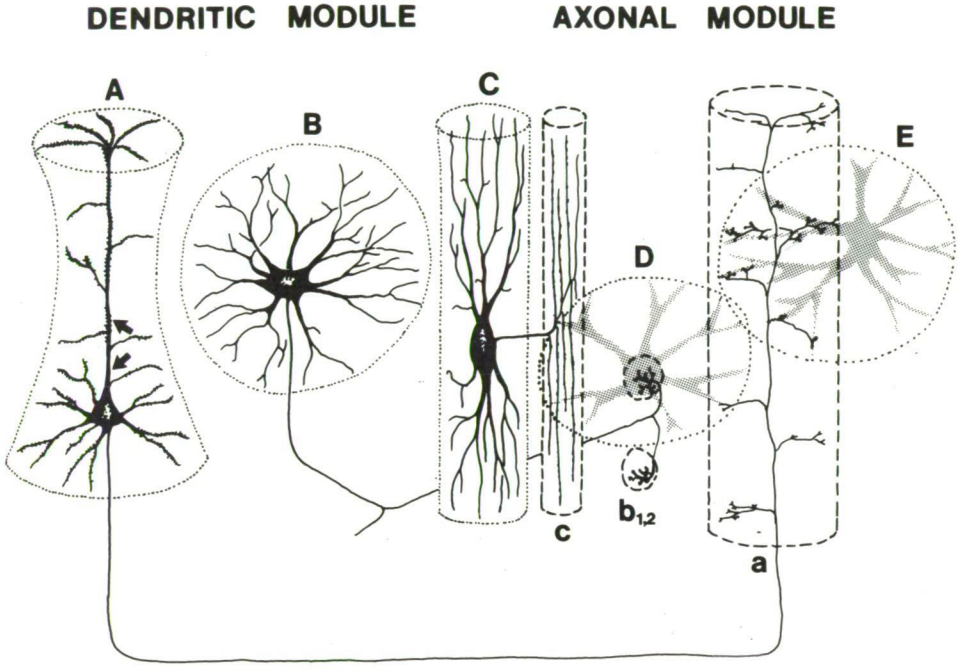

Fig. 2: Neurons can be classified according to the size, shape and position of their "dendritic" and/or "axonal modules". Projection neurons (A) have long axons and make synaptic contacts to target cells in remote positions (synapses of A and E). Local interneurons (B, C) have short axons and may focus their synapses on specific target cells, e.g. „basket cells" which effectively inhibit other neurons at their perikaryon (synapses of B on D).

— Statistically, each neuron is connected to an extremely small subpopulation of all neurons (mammalian brains contain 10^7 to 10^{11} neurons; each neuron forms and receives 10^0 to 10^4 synapses; the ratio between connected and unconnected neurons is therefore probably smaller than 1:1 million).

— Neuron classes can be defined by the size and shape of their "receiving cables" and/or "transmitting cables" (see Figs. 1 and 2).

— Projection neurons have long axons establishing synaptic contacts to specific target cells in remote positions (neuron A in Fig. 2).

— Local interneurons have short axons selectively innervating specific neighbouring cells but avoiding others (e.g. "basket cells", neuron B in Fig. 2).

— There are often countercurrent connections between neurons in different parts of the nervous system (see Fig. 3).

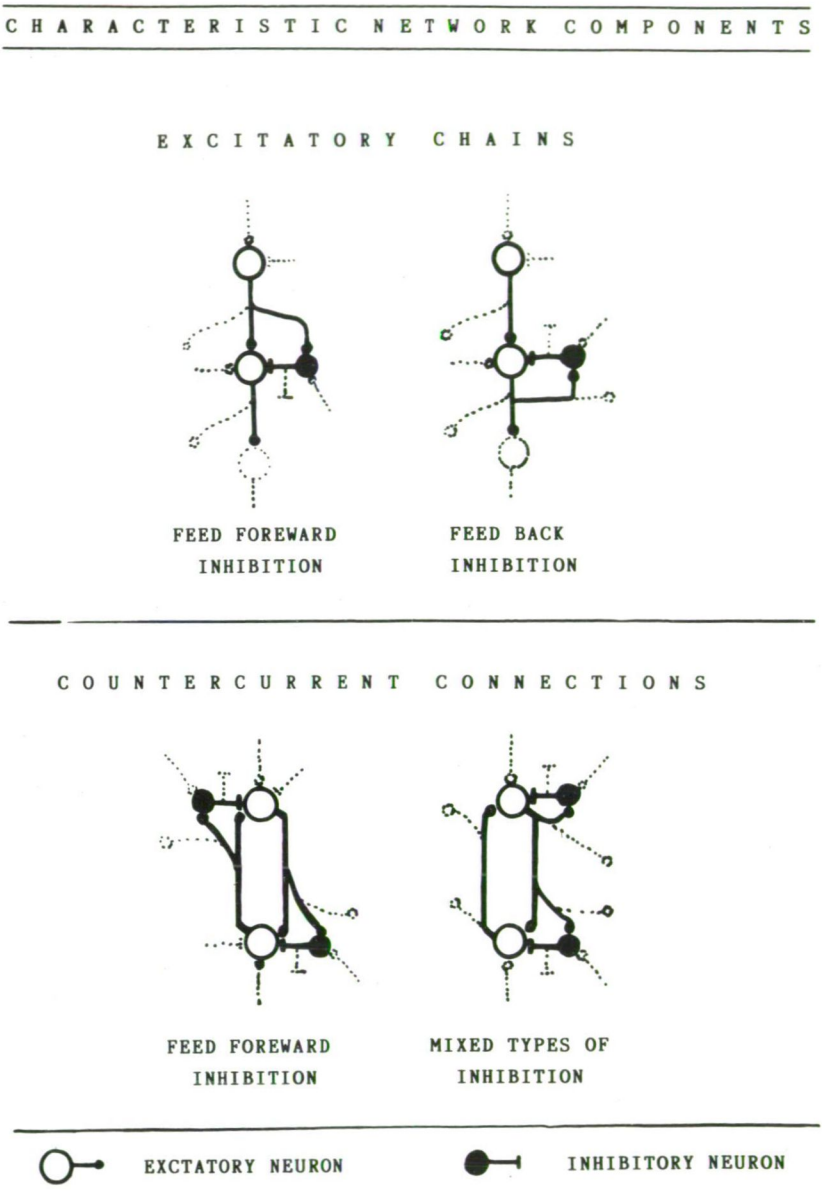

Fig. 3: Characteristic constellations of excitatory and inhibitory neurons which can be isolated from complex networks in the nervous systems. Note the characteristic involvement of various types of feed-forward- or feedback-inhibition. Dotted lines represent disregarded connections.

Thus, neuronal connections are selective, i.e. they are restricted to extremely small subpopulations of all neurons. Some of them are apparently specific, because they are focused on specific partner cells.

The third suggestion is that *neurons participate in the choice of their communication partners.* This assumption is supported by experimental evidence. During ontogenesis, synaptic connections primarily show a relatively diffuse distribution but are secondarily specified. This remodelling is often based on selective elimination of synapses (Fig. 4.). On the other hand, selective sprouting of axons is observed when synaptic connections are lost (e.g. after lesions; Fig. 5). Reactive synaptogenesis reveals that a hierarchy exists in the specificity of neuronal connections. Thus, neurons are apparently involved in the choice of communication partners. The choice may be based on selective formation and/or elimination of synaptic connections.

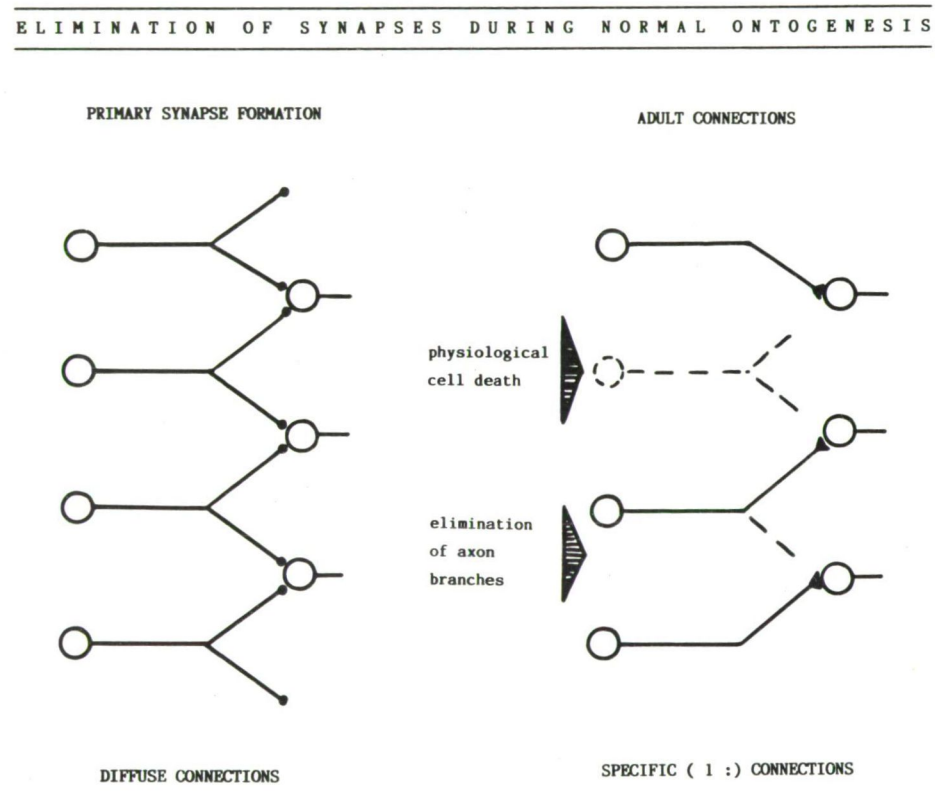

Fig. 4: During ontogenesis, many connections between sets of neurons are secondarily specified by elimination of inappropriate connections. This may be based on a loss of axon collaterals, but may also include cell death of significant fractions of neurons. Thus, brain development shows critical periods of synaptic reorganization. These may result in „catastrophies" on the level of cells or networks and apparently serve to stabilize the surviving connections.

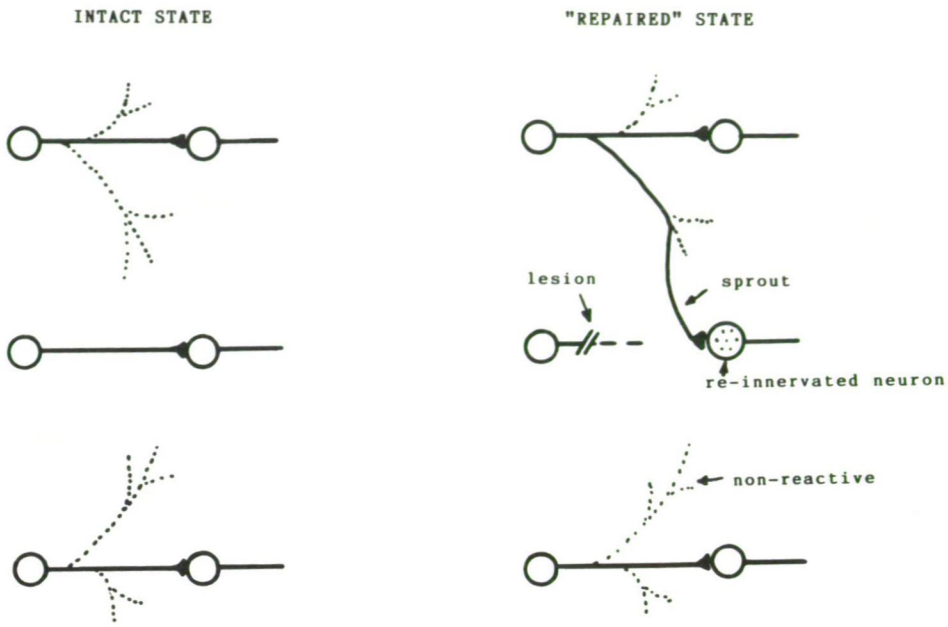

Fig. 5: In the adult nervous system, experimental lesions or pathological processes may induce synapse degeneration. This in turn results in synaptic reorganization, which may include selective sprouting of some axon types, while others do not react at all. Thus, re-innerveration is a selective process. Reactive synaptogenesis reveals a hierarchy of compensatory mechanisms which regulate the connectivity of the nervous system.

Now, we may ask the main question: *What are the conditions on which neurons form and stabilize connections to other neurons?* We have seen that each synapse consists of pre- and postsynaptic elements. In certain conditions, however, one can observe supernumerous ("free" or "vacant") presynaptic or postsynaptic elements which did not find appropriate contact partners. This finding indicates that pre-and postsynaptic elements may be formed or eliminated independently from each other. Therefore, the stabilization of a synapse seems to depend on proper conditions in both the presynaptic neuron and the postsynaptic neuron. We then have to specify our question by asking: What are the conditions in which neurons form and maintain presynaptic or postsynaptic elements? And are these conditions different for excitatory and inhibitory synapses?

In vivo and vitro experiments suggest that increased excitation of neurons stimulates the *formation of presynaptic elements.* In addition, there is indirect evidence that loss of inhibition may have a similar effect as increased excitation. On the other hand, increased inhibition and a loss of excitation may reduce the growth of axons and, therefore, reduce the number of presynaptic elements. At present, there is no evidence that excitatory and inhibitory neurons react in a different manner (Fig. 6).

RESPONDING SYNAPSE COMPONENT		CHANGES IN INPUT E↑	I↓	E↑	I↓
presynaptic elements	E	+	(+)	−	−
	I	+	(+)	−	−
postsynaptic elements	E	−	(−)	+	+
	I	(+)	(+)	−	−
		E/I ↑		E/I ↓	

On the other hand, are there conditions that promote the *formation of postsynaptic elements?* We know very little about the dynamics of postsynaptic elements of *inhibitory* synapses. These synapses tend to accumulate on perikarya and on proximal dendrites rather than on peripheral ones. This distribution pattern indicates that inhibitory postsynaptic elements increase in number where excitatory postsynaptic potentials converge and summate. On the other hand, there are reports on hypersensitivity for inhibitory transmitters developing as a consequence of decresased or lost inhibitory input. These have been tentatively summarized as shown in the last row of Fig. 6.

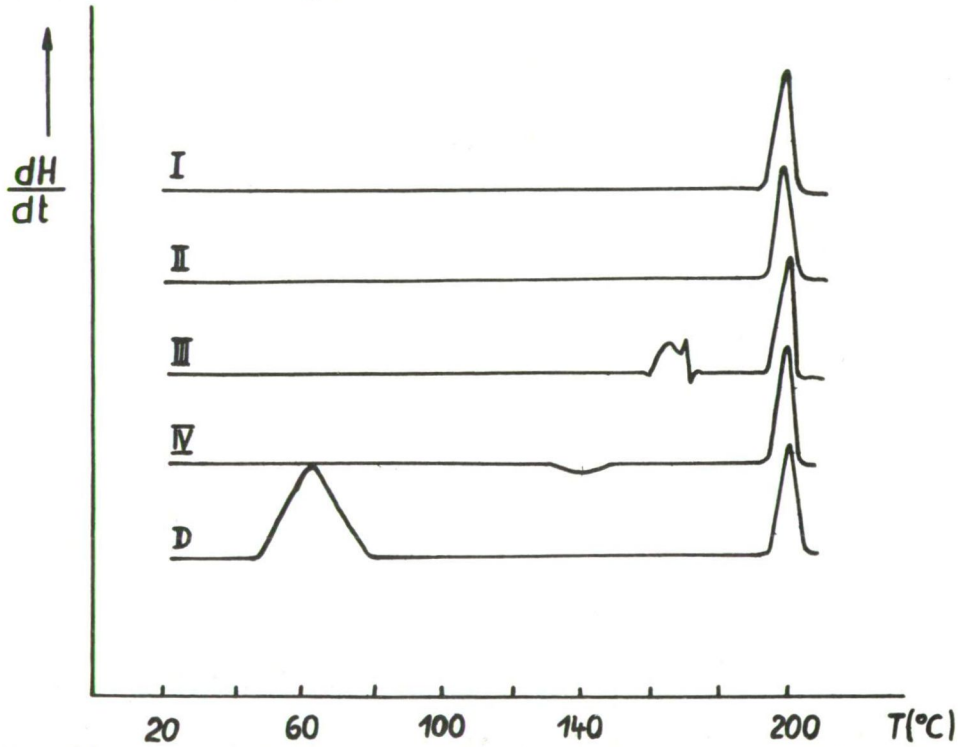

Fig. 6: Scheme of synaptic plasticity reactions following longterm disturbances of the excitation/inhibition balance (E/I). These reactions may be induced by changes in input (E ↑, ↓; I ↑, ↓) but also by other factors such as certain hormones, growth promoting factors, etc. (not included). "Plus": increase in number or efficacy of pre- or postsynaptic elements, i. e. their formation is promoted and/or their breakdown is diminished. "Minus": decrease in number or efficacy of synaptic elements, formation retarded and/or breakdown increased. Brackets indicate that direct experimental evidence is not yet available, but circumstantial evidence exists (for details see Wolff und Wagner, 1983; Dammasch et al. 1986; Wagner and Wolff, 1988).

Vacant *postsynapic densities of excitatory* synapses transiently occur in various parts of the nervous system. Experimentally, their appearance can be induced by lesions which destroy excitatory axon systems. Thus, when the excitatory input decreases vacant postsynaptic elements for making excitatory synapses appear (Fig. 6). Since inhibition can decrease the efficacy of excitatory input in postsynaptic neurons, one may wonder whether increased inhibition affects the number of "vacant" (excitatory) postsynaptic elements in a similar manner as reduced excitation.

At this point, I shall briefly summarize some results which were obtained in a long lasting cooperation with colleagues from Szeged (listed below).

Co-workers in Szeged

JOO, F. HALÁSZ, N. PÁRDUCZ, Á. SIKLÓS, L.	Biological Research Center (Molecular Neurobiology Unit)
KÁSA, P. DOBÓ, E. GULYA, K. RAKONCZAI, Z.	Szent-Györgyi Albert Medical University (Central Research Laboratory)
FEHÉR, O. TÓLDI, J. ROJIK, I.	Attila József University (Dept. of Comparative Physiology)

Co-workers in Göttingen

BALCAR, V. J. DAMES, W. DAMMASCH, I. HOLZGRAEFE, M. LEUTGEB, U. MICHLER, A. RICKMANN, M. WAGNER, G.	Georg August University (Dept. of Anatomy and Neurology)

For most of these multidisciplinary studies, we selected the superior cervical ganglion. In rats, this ganglion contains a relatively small set of neurons which receive excitatory input via acetylcholinergic axons from the spinal cord. The principal ganglion cells provide the sympathetic (noradrenergic) innervation to the head region. It was demonstrated that, apart from other interneurons, this ganglion includes GABAergic components. These are driven by preganglionic input and inhibit the principal ganglion cells (Fig. 7A, Wolff et al., 186; Kása et al., 1988). The

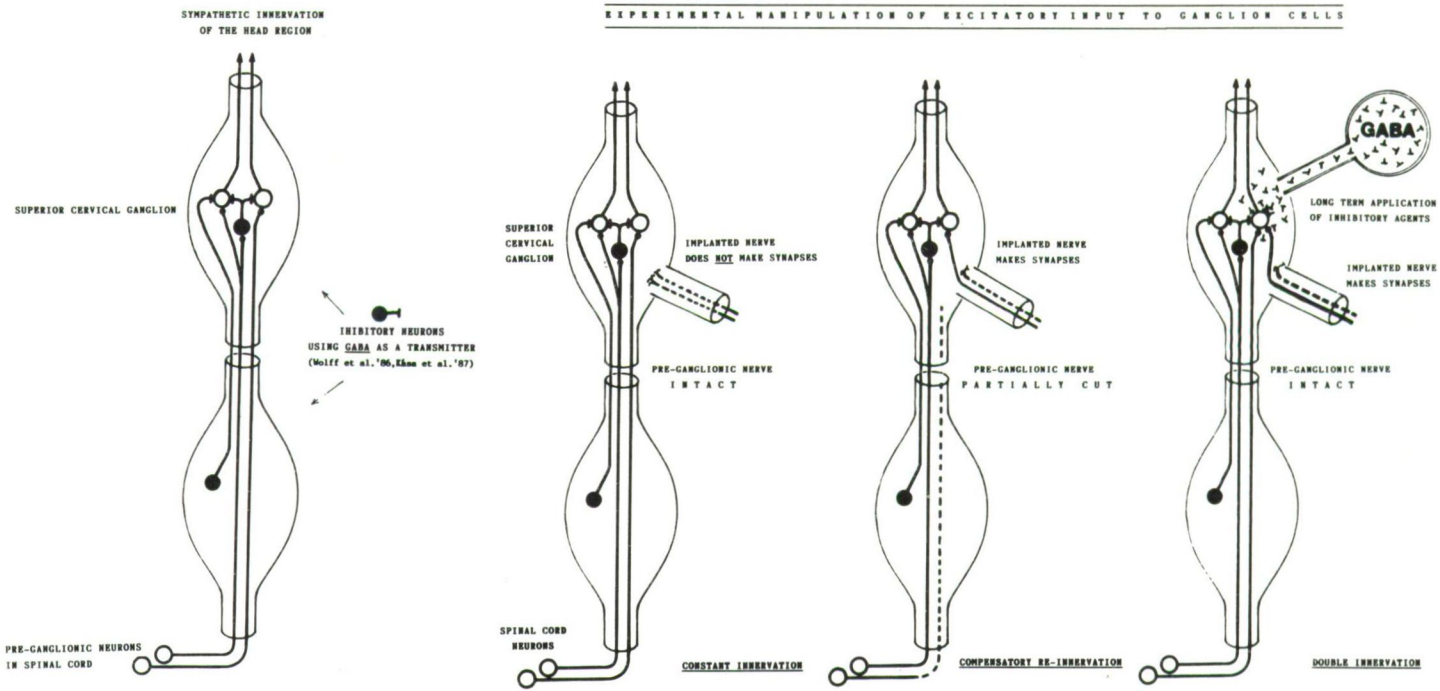

Fig. 7: Scheme of synaptic components and neuroplastic reactions in the superior cervical ganglion of rats. *A:* normal ganglion (SIF cells and other interneurons are not shown); *B:* foreign nerve implanted into the normal ganglion is not able to make functional synapses; *C:* after partial de-afferentation (interruption of preganglionic axons) implanted acetylcholinergic nerves do make functional synapses on principal ganglion cells; *D:* a surplus of inhibition induced by exogenous GABA provides conditions in which implanted nerves do make synapses in the presence of intact preganglionic nerves.

existence of an endogenous GABA-system may explain why externally applied GABA (gamma- aminobutyric acid) strongly inhibits the activation of ganglion cells when the preganglionic nerve trunk is stimulated (Farkas et al., 1986).

The superior cervical ganglion was a suitable model for our experiments, (review see Wolff et al., 1987) because it had been previously demonstrated that the hypoglossal or vagal nerve can be implanted in vivo into this ganglion. We confirmed that the foreign nerve does *not* make synapses in this ganglion as long as the preganglionic nerve is intact (Fig. 7B). We also confirmed that the implanted nerve does, however, make functional (acetylcholinergic) synapses on ganglion cells when the preganglionic nerve had previously been cut, at least partially (Fig. 7C). Interestingly enough, long-term application of exogenous GABA induced the formation of vacant postsynaptic densities for excitatory synapses. In addition, the number of acetylcholin-receptors transiently increased ("hypersensitivity), if GABA was infused into ganglia with an intact preganglionic nerve. In other words, if none of the above-mentioned nerves was implanted in addition to the GABA-applicator, the nerve was able to make functional synapses on ganglion cells, although the preganglionic nerve was intact (Fig. 7D). This indicates that both decrease of excitatory input and hyperinhibition have a similar effect on the acceptance of excitatory synapses (Fig. 6).

In both cases, the formation of synapses depends on additional (acetylcholinergic) presynaptic elements provided by the implanted (regenerating) nerve. Viewed from the level of the organism, the „double innervation" of a sympathetic ganglion by a preganglionic sympathetic nerve and a motor nerve (hypoglossal n.) or a parasympathetic nerve (vagal n.) does not make sense. At the cellular level, however, ganglion cells may overcome hyperinhibtion by additional excitatory input. This indicates that the amount of pre- and/or postsynaptic elements formed and stabilized by neurons depends on local conditions. If these conditions change, neurons will show plastic reactions and the synaptic connections will be reorganized, if appropriate partners can be found.

This "trophic" effect of hyperinhibition is not specific for GABA. Similar plastic responses may be induced by long-term application of sodium bromide (NaBr, „tranquillizer of the 19th century") which does not require local application, but is taken orally via the drinking water in therapeutic-like doses (140—280 μg/l). Thus, synaptic plasticity can also be induced by long-term pharmacotherapy of drugs which increase neural inhibition.

In normal conditions, inhibition and excitation of neurons mainly depends on synaptic input (and in some cases on hormonal effects). Synaptic input is regulated by transneuronal interactions. In Fig. 8A–C it is demonstrated how such transsynaptic effects might influence the formation and stabilization of synapses. Probably, such mechanisms are also involved in normal synapse formation, because characteristic combinations of excitatory and inhibitory neurons are found in the brain and spinal cord (Fig. 3).

We may *summarize* this view of how neurons choose communication partners, as follows:

— The choice of communication partners is based on selective stabilization and breakdown of synapses.

— In each neuron, the balance between excitation and inhibition plays a role in the stabilization or elimination of synapses.

— A neuron may distinguish between "good" and "bad" synapses depending on whether they stabilize or disturb the balance.

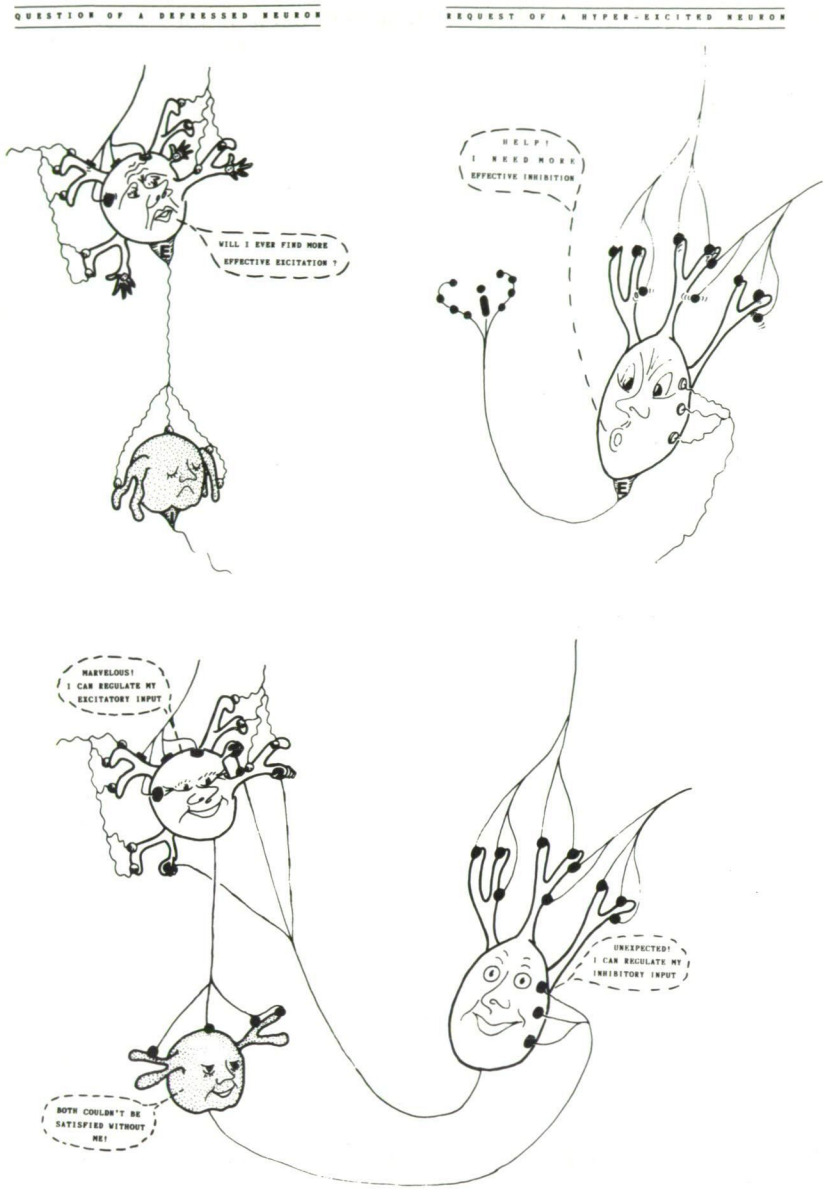

Fig. 8: Cartoon-like illustration of how neurons may cooperate in the formation and stabilizion of synaptic connections within small networks.

— In this way, each neuron may choose communication partners because of their local effects.

— Since synaptic effects depend on cell-to-cell interactions in neuronal networks, synapse formation can compensate disbalanced states of neuronal networks, and vice versa.

— In this way, synaptic connections may be adapted to the requirements of the nervous system and may be modified by sensory input, although their formation and maintenance is based on local decisions.

— We may conclude that the choice of communication partners in the nervous system is itself a result of communication between neurons and neuronal networks.

Implications and applications of this concept

It is proposed that synaptic connections are formed, maintained or eliminated according to rules which tend to compensate disturbances of the excitation-inhibition balance of the neurons concerned (see Fig. 6). The rules are based on extreme simplifications and their experimental basis is still imcomplete. The heuristic value of such a working hypothesis obviously depends on whether or not it leads to new approaches to the nervous system. Here, I shall focus on four aspects of neurobiology:

Basic research: It is difficult to study interaction mechanisms in complex systems. One of the major obstacles is that experiments require identical reproduction which can hardly be achieved in complex interactive systems. One way to overcome this restriction is the formalization of theories followed by computer simulation. Biological experiments may then be restricted to testing critical predictions from "simulated experiments". This can be done with the "compensation theory of synaptogenesis" (see Wolff and Wagner, 1983; Dammasch et al., 1986).

Ontogenesis: It is one of the challenges of developmental neurobiology to explain the interaction between genetic information and epigenetic mechanisms. The concept predicts that brain development is regulated by at least three types of factors: (1) Trophic factors comprise all agents and conditions (including synaptic input) which affect any part of the molecular cascade which leads to formation or breakdown of pre- or postsynaptic elements and/or synaptic contacts; (2) spatial and temporal maturation patterns of excititatory and inhibitory neurons; (3) environmental factors include not only information transfer from sensory organs and noxious influences on the formation or stabilization of synapses.

Pathology: The concept claims that the stability of connections in the normal brain results from a dynamic equilibrium of productive and degrading mechanisms. Following lesions, we will have to identify different conditions in which synaptic reorganization either results in functional rehabilitation or leads to progressive dysfunction (degenerative diseases).

Pharmaco-therapy: According to the compensation theory of synaptogenesis, we have to be aware of the possibility that synaptic connections may be modified by long-term application of drugs which interfere with synaptic transmission.

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